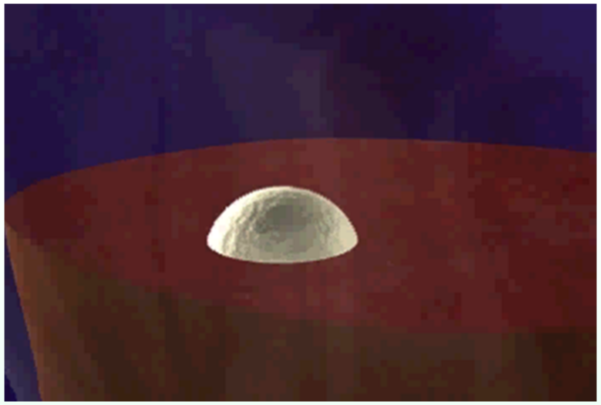
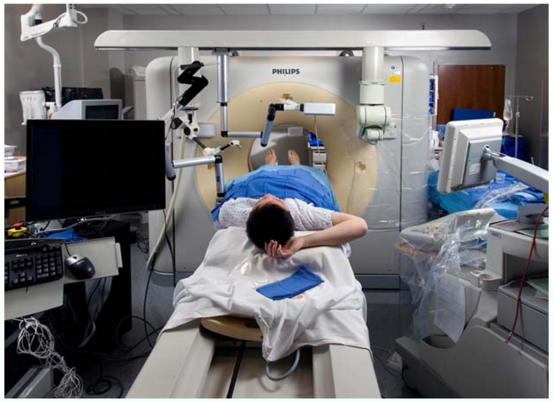
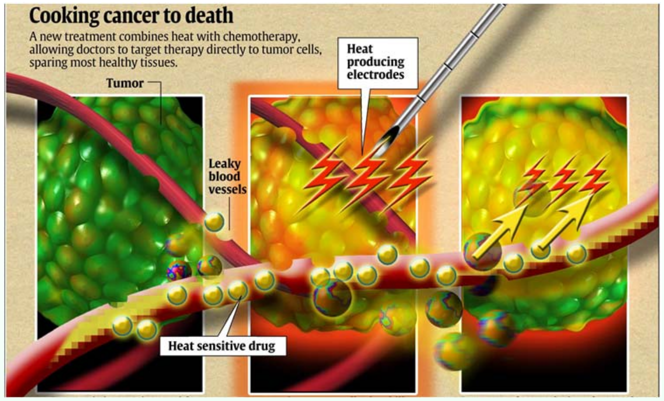




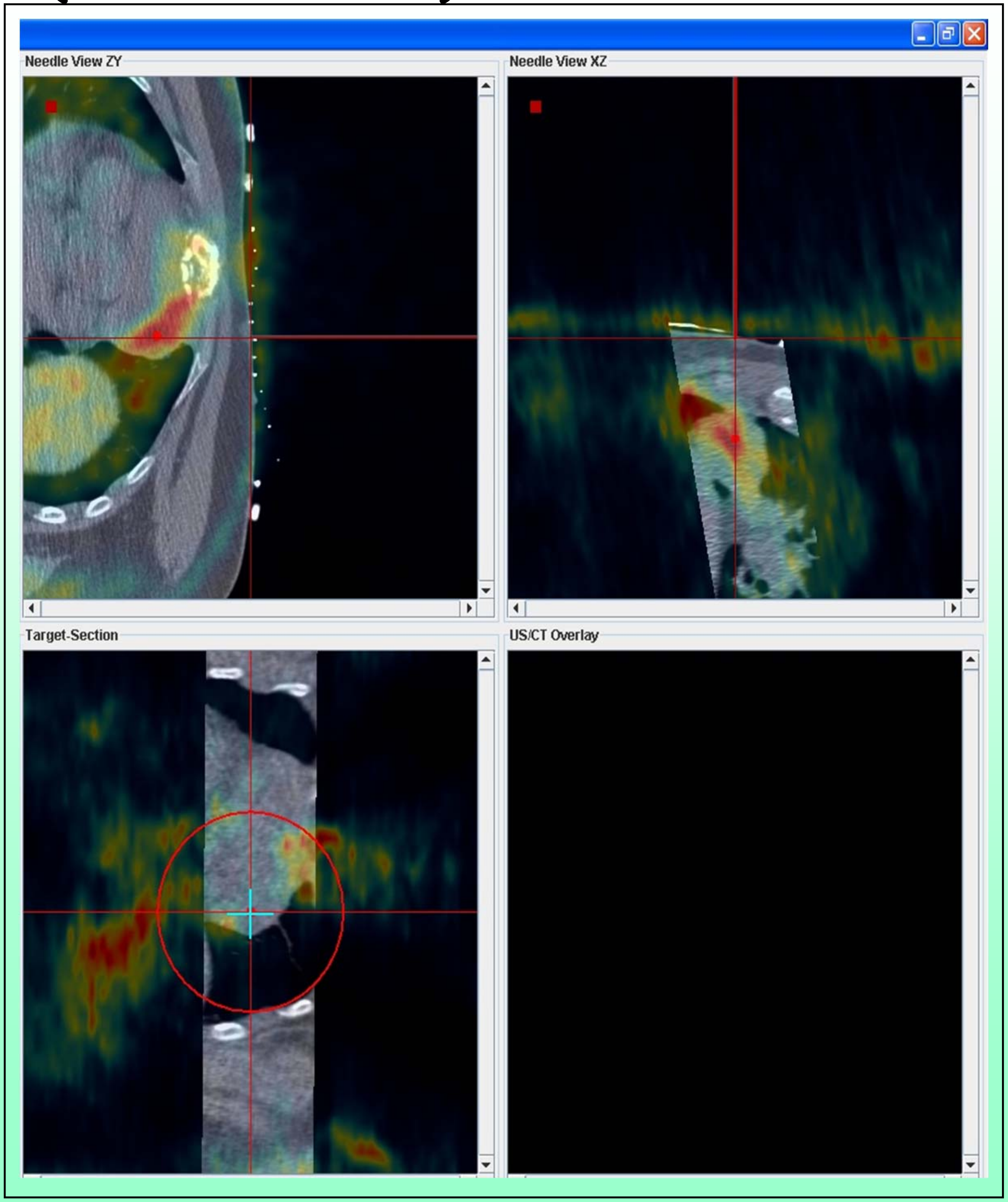


Imaging and Multi-modality Navigation in Interventional Oncology

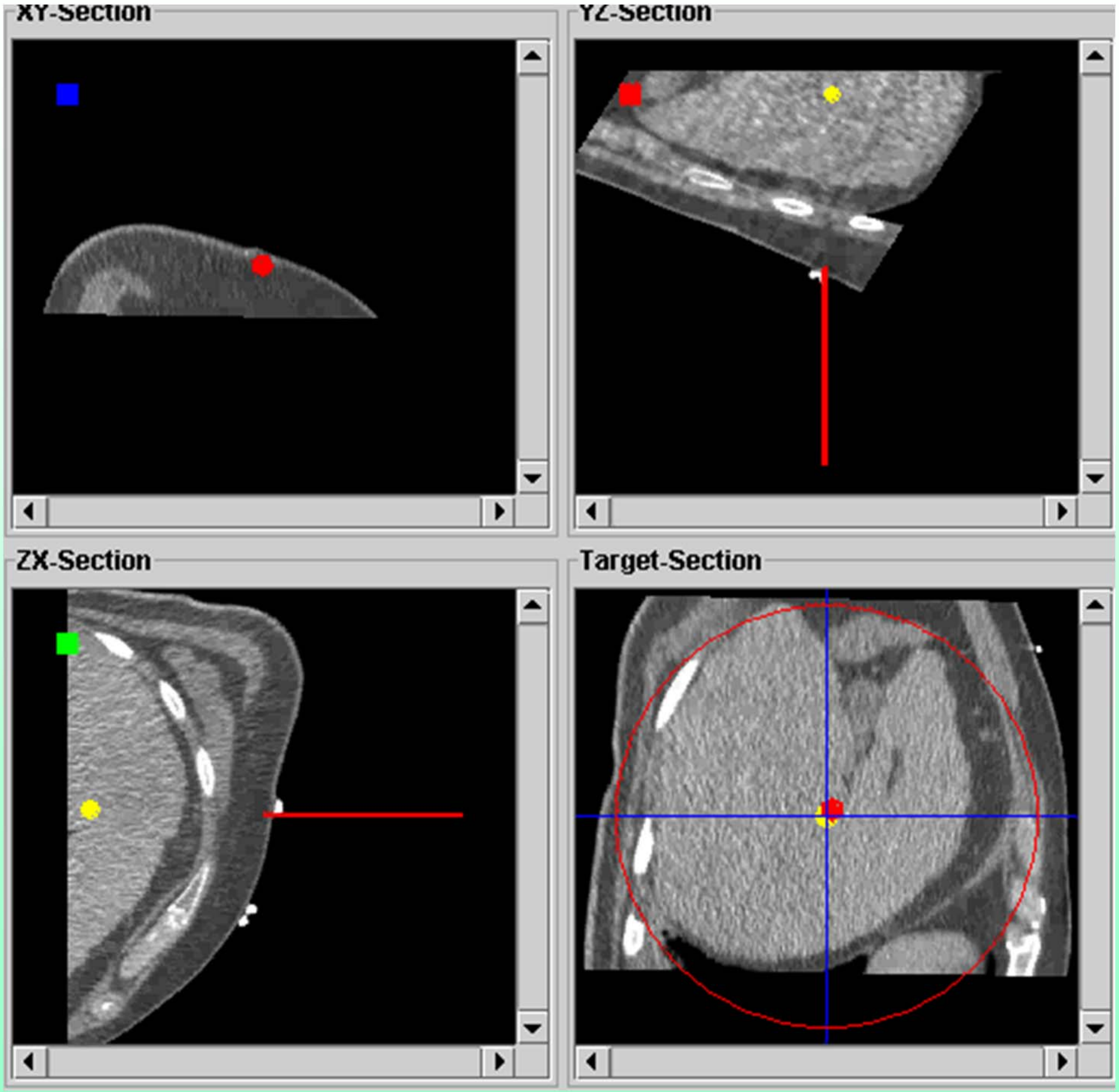
- Molecular Interventions:
    - Drug + Device + Image
- Multi-modality Interventions:
    - Medical GPS during procedures
- Operating Room of Future:
    - Navigation & Robots
    - Personalized Oncology
    - Image-Guided Drug Painting

Brad Wood, MD
NCI Center for Interventional Oncology
Intramural Research Program
NCI BSA, October, 2009

PET (Metabolic) Guided Procedures



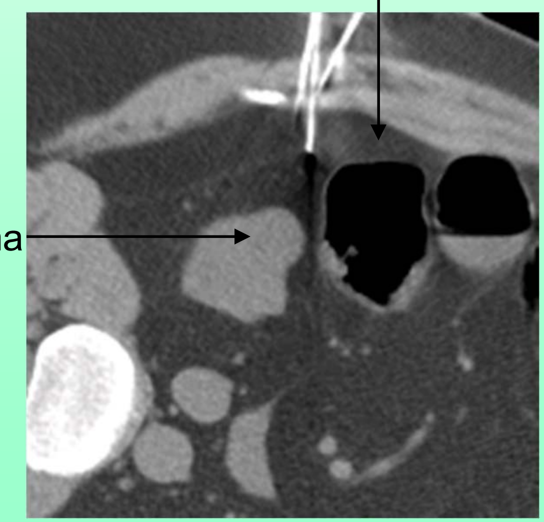
Closing the Gap Between Diagnosis & Therapy

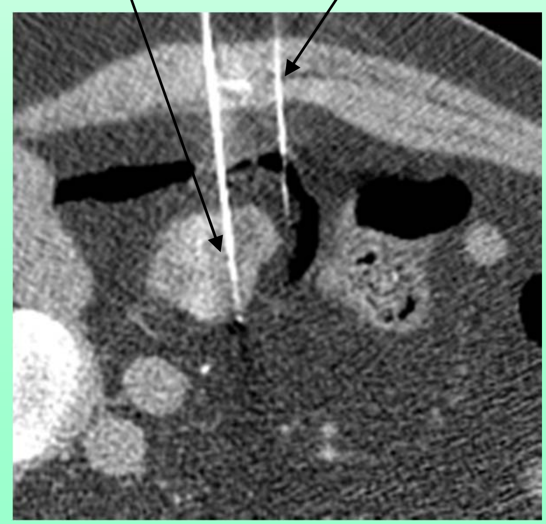


Minimally Invasive & Image Guided:
Convergence of Devices & Imaging

Tumor Ablation
Uterine Fibroid Embolization
Stent Grafts
Brain Aneurysm Coiling
Vertebroplasty
Balloon Angioplasty
Venous Ablation
Carotid Stenting

} Less Surgery

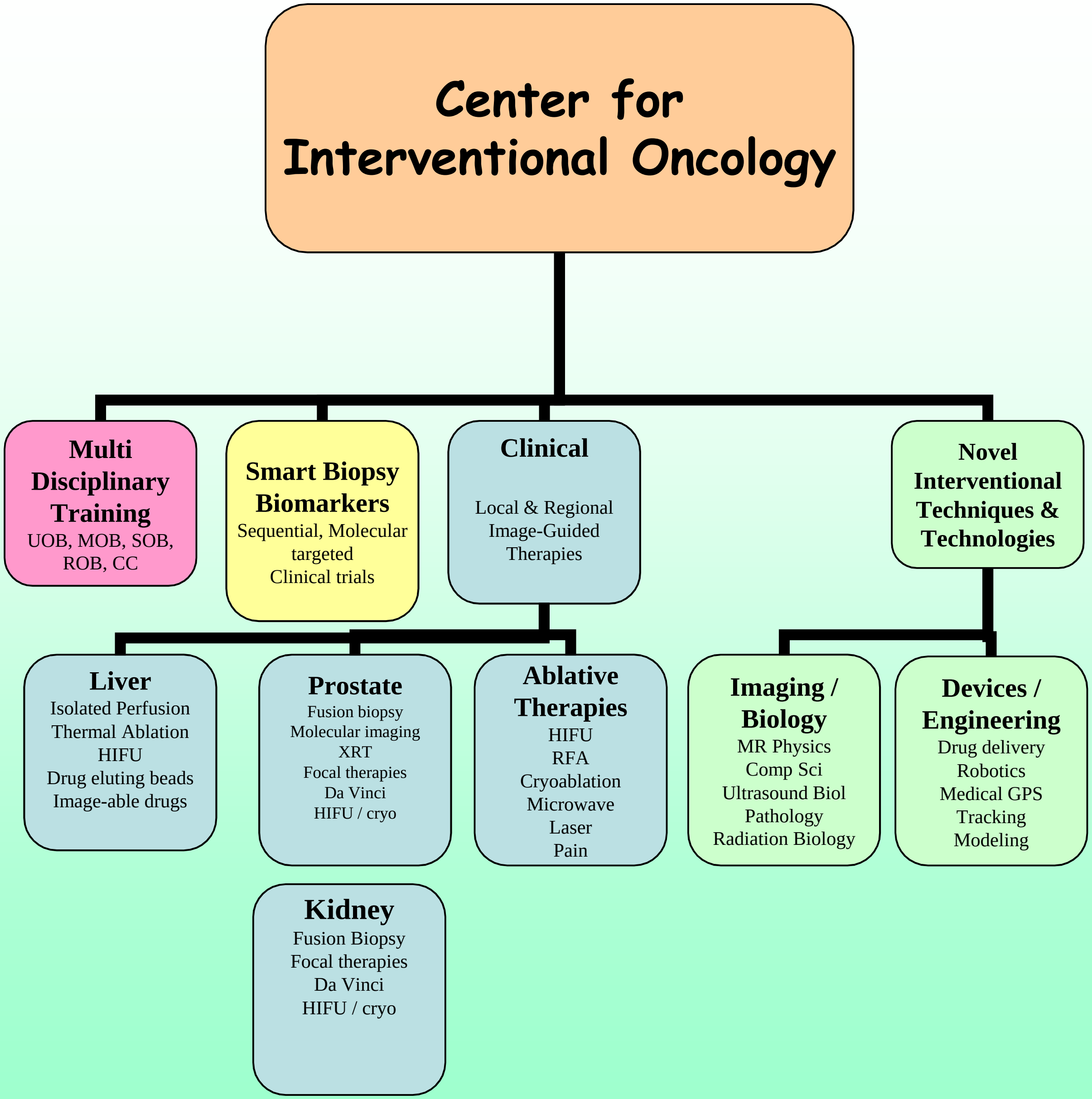




Center for Interventional Oncology

Mission

- Close gap between Diagnosis & Therapy
- Establish a collaborative environment to bring together multidisciplinary partners to help define minimally-invasive image-guided methods for tx of locally-dominant cancer

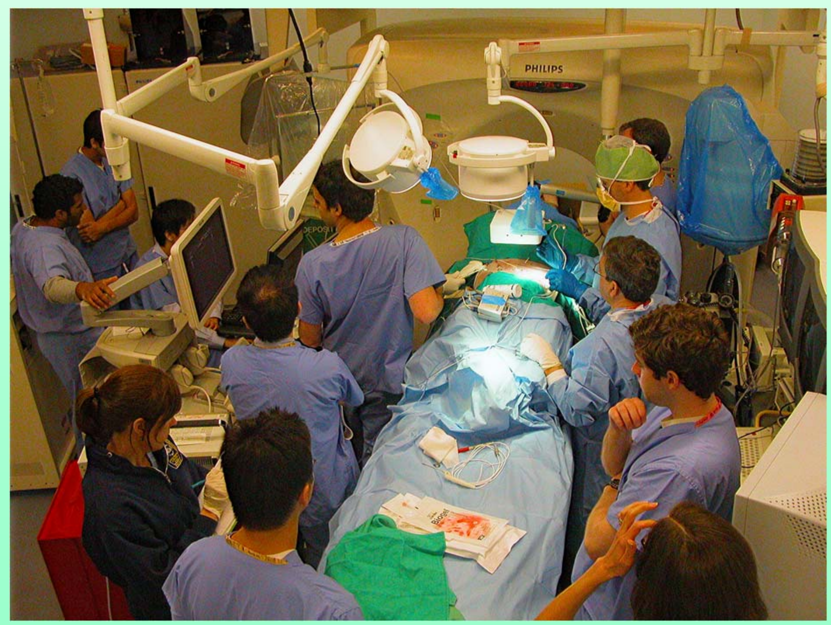


Center for Interventional Oncology
Multi Disciplinary Training
UOB, MOB, SOB, ROB, CC
Smart Biopsy Biomarkers
Sequential, Molecular targeted Clinical trials
Clinical
Local & Regional Image-Guided Therapies
Novel Interventional Techniques & Technologies
Liver
Isolated Perfusion
Thermal Ablation
HIFU
Drug eluting beads
Image-able drugs
Prostate
Fusion biopsy
Molecular imaging
XRT
Focal therapies
Da Vinci
HIFU / cryo
Ablative Therapies
HIFU
RFA
Cryoablation
Microwave
Laser
Pain
Imaging / Biology
MR Physics
Comp Sci
Ultrasound Biol
Pathology
Radiation Biology
Devices / Engineering
Drug delivery
Robotics
Medical GPS
Tracking
Modeling
Kidney
Fusion Biopsy
Focal therapies
Da Vinci
HIFU / cryo

Collaborative Network:

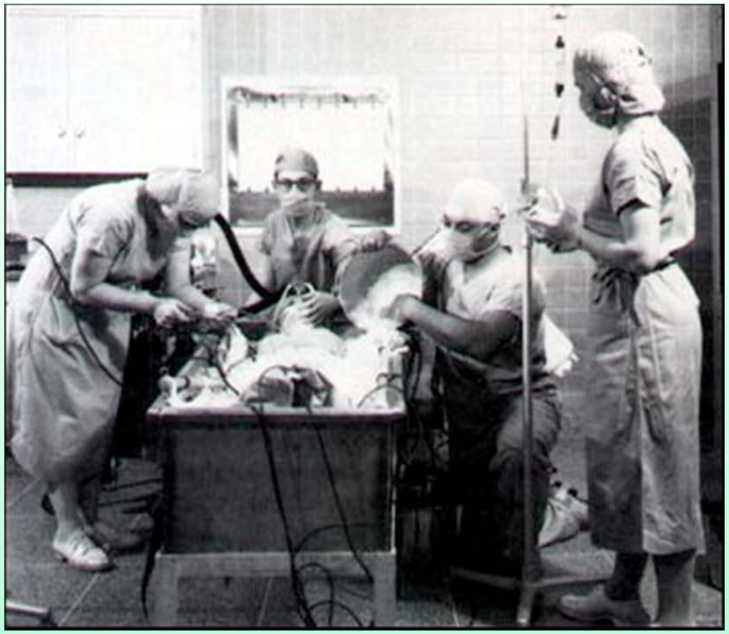
Interdisciplinary
Inter-agency
Translational
International

Industry / Extramural Academic / Government

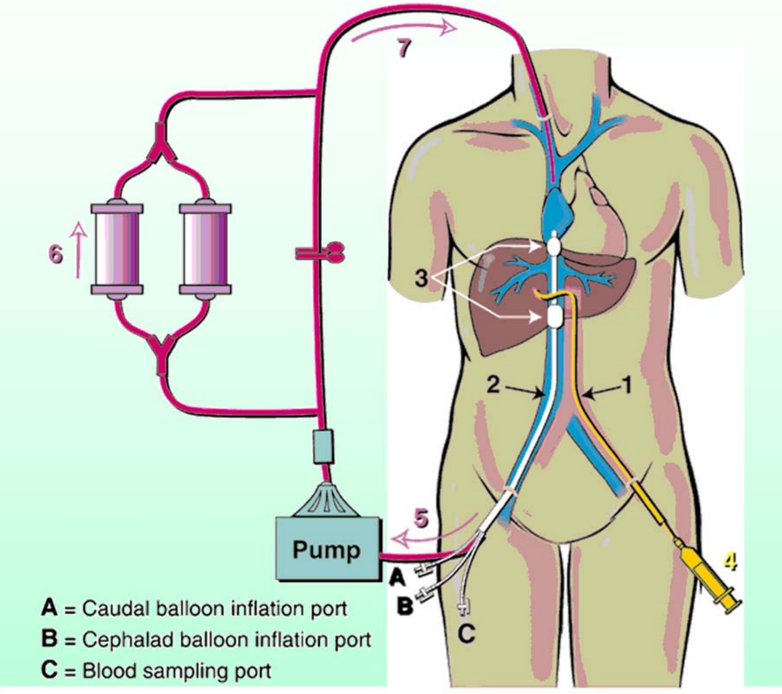


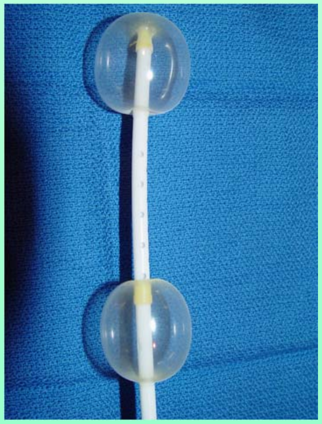
http://www.cc.nih.gov/centerio/index.html

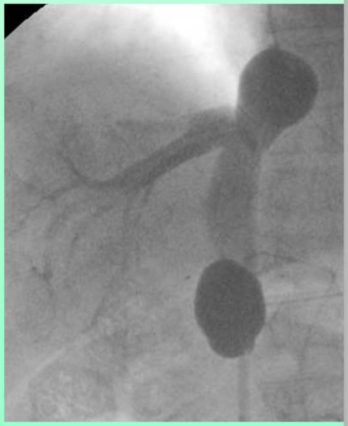
1955 NIH:
Open Heart Surgery
w/ Extra-Corporal Circuit

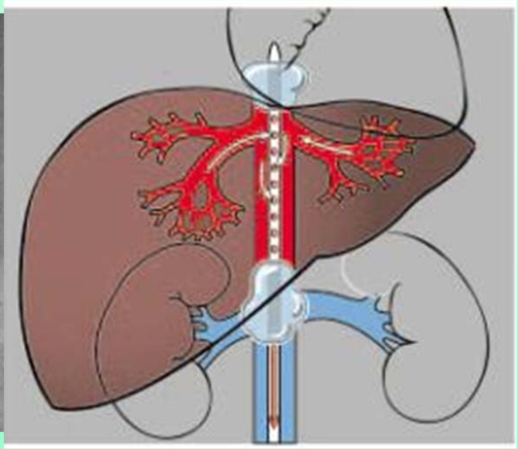


2009 NIH:
Percutaneous Liver Perfusion









~300 PHP's in 120 pts
80% response rates for
neuroendocrine & ocular melanoma

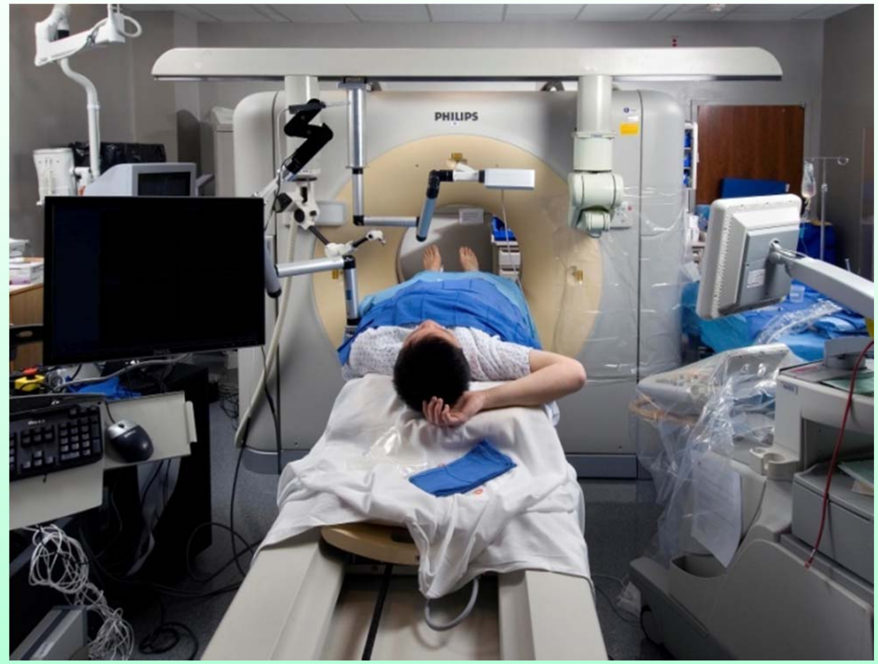
Imaging and Multi-modality Navigation in Interventional Oncology

Overview

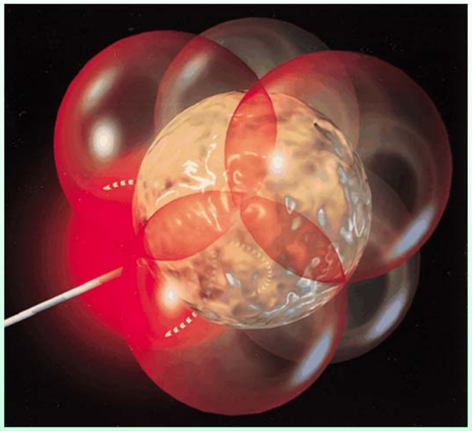
- "Molecular Interventions":
  - Drug + Device + Image
- Multi-modality Interventions:
  - Medical GPS during procedures
- Operating Room of Future:
  - Navigation & Robots
  - Personalized Local & Regional Oncology
  - Image-Guided Drug Painting:
    - RFA + heat-deployed liposomal drug
    - Image-able drug eluting bead + RFA
    - HIFU + heat-deployed liposomal contrast + drug

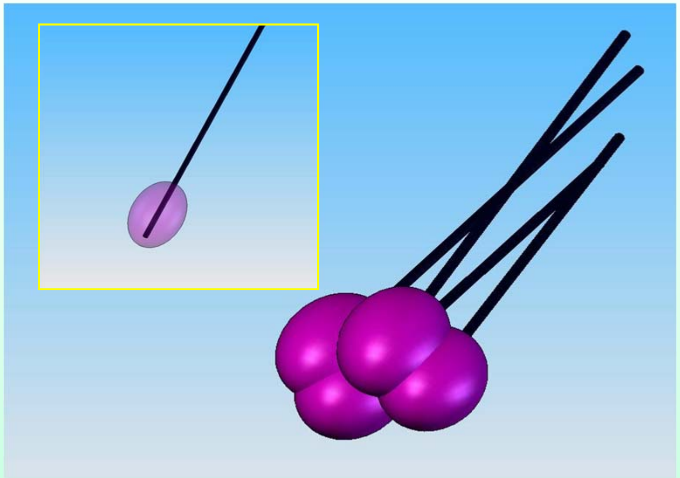
Early 20th Century
Stereotactic Frame

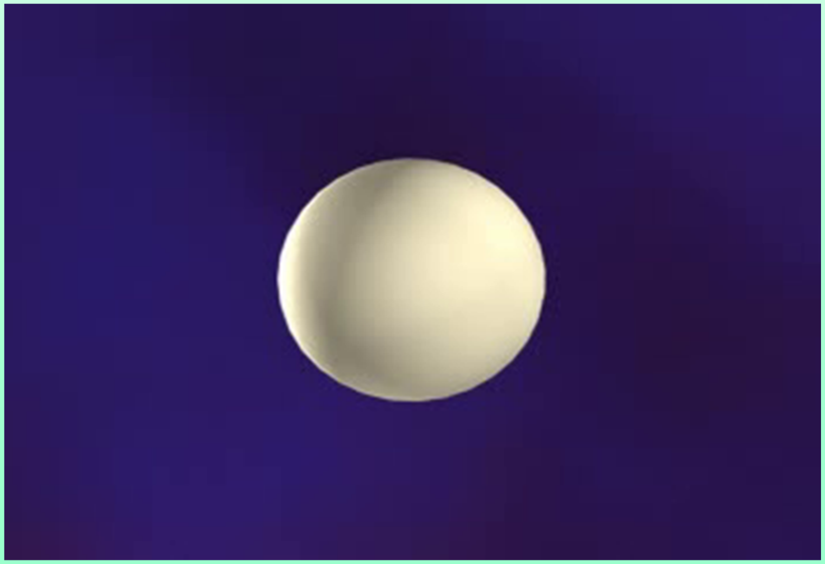
2009 NIH:
Medical GPS devices,
Fusion-guided procedures,
Image-guided robotics

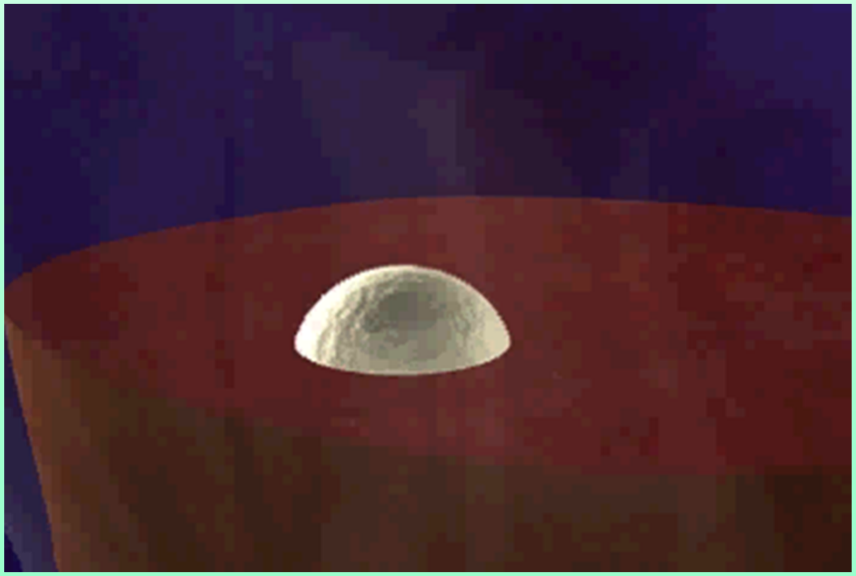


Needle Ablation Complex Geometries: Outcomes Depend Upon Accuracy

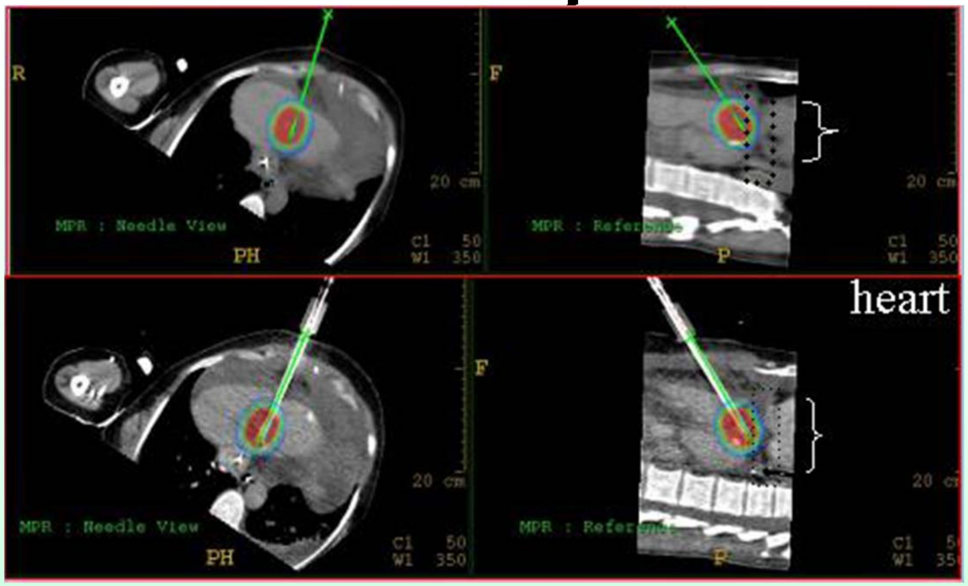






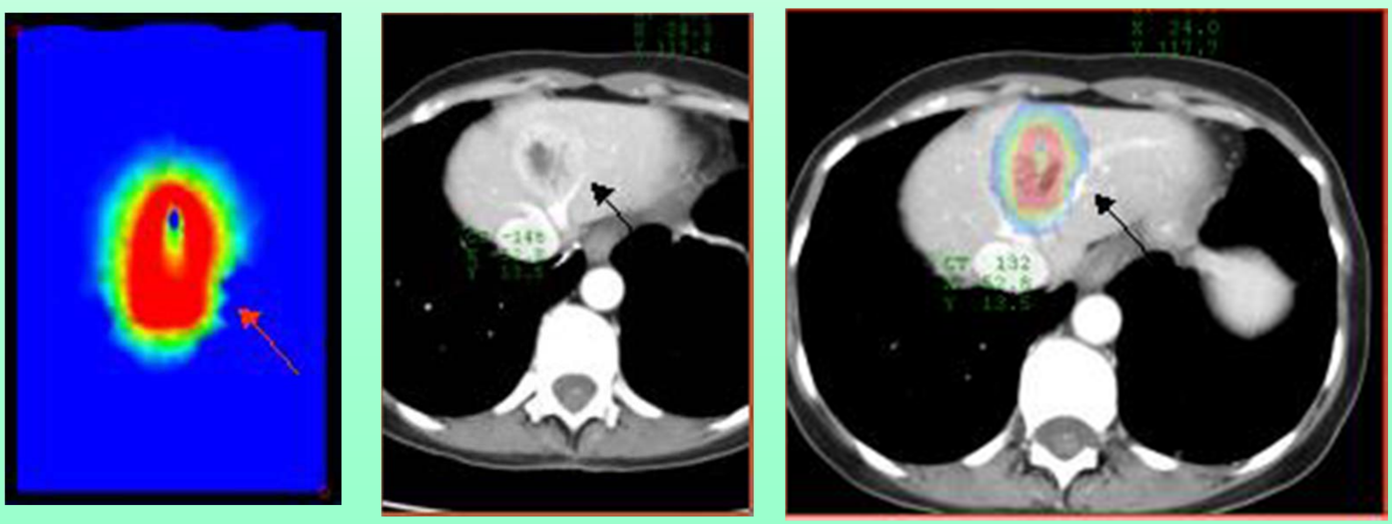


Patient-Specific Treatment Plans

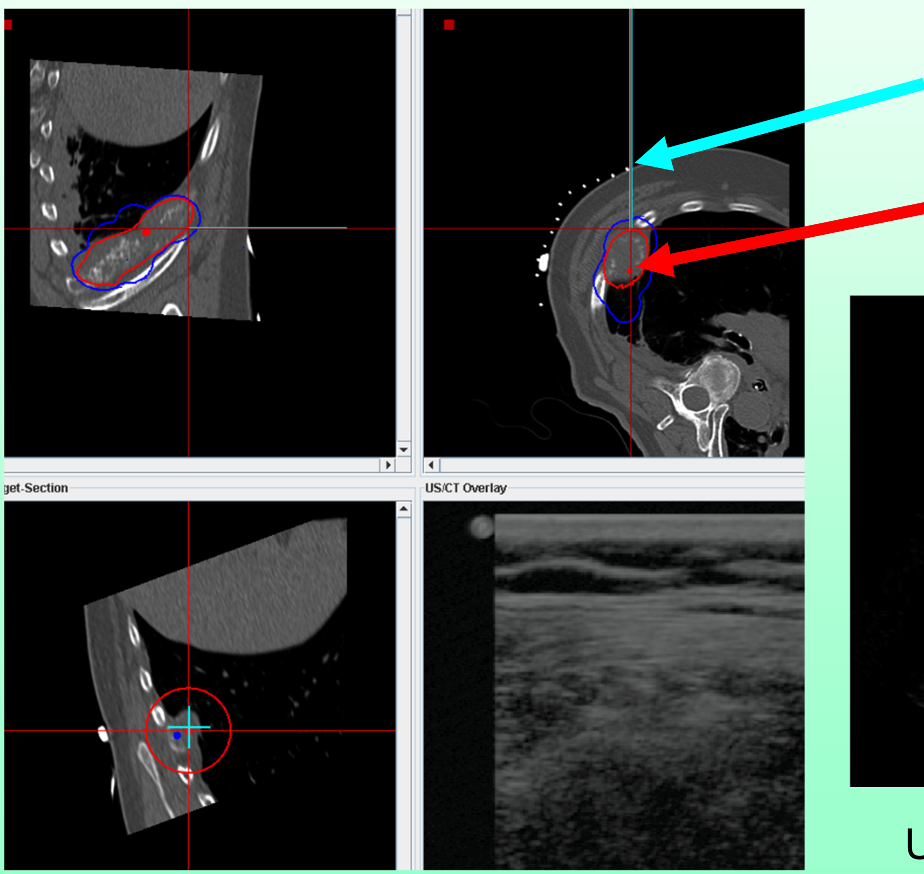


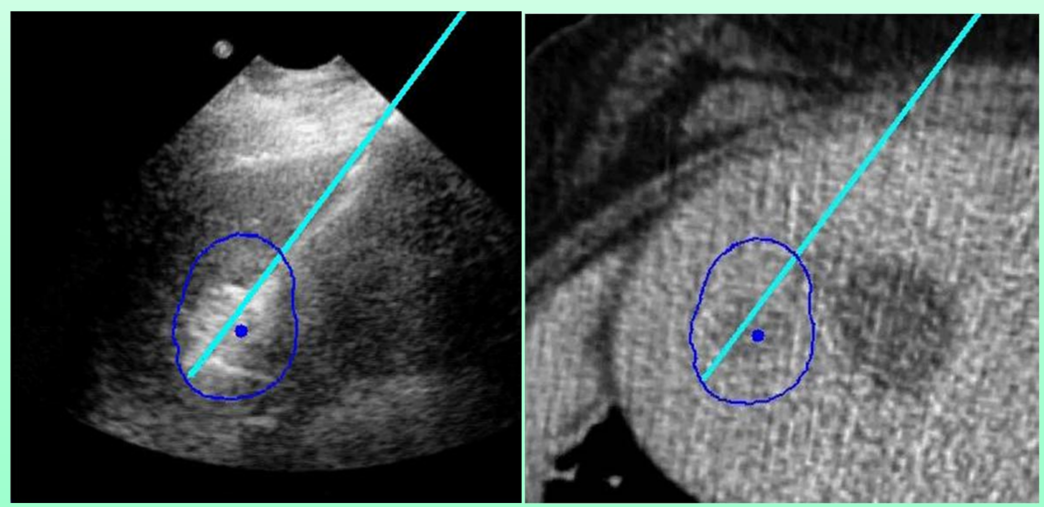
Risk to Adjacent Anatomy (Heart)

Risk of Heat Sink



- Automated RFA planning tool integrated with navigation

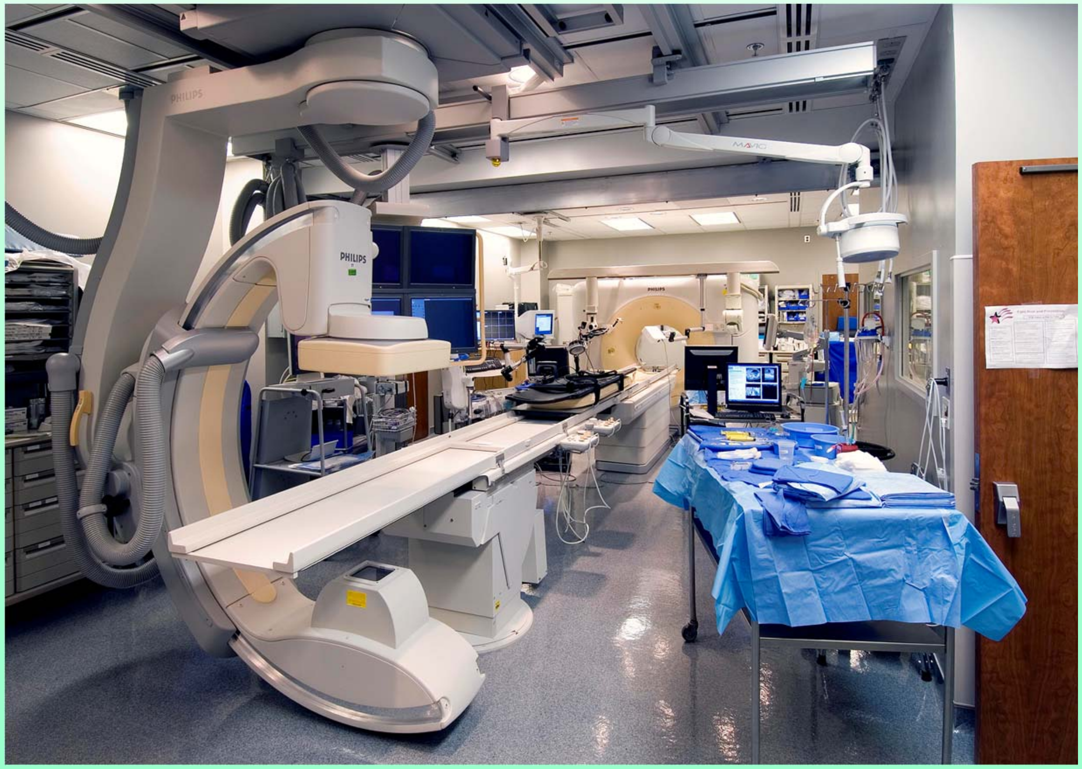




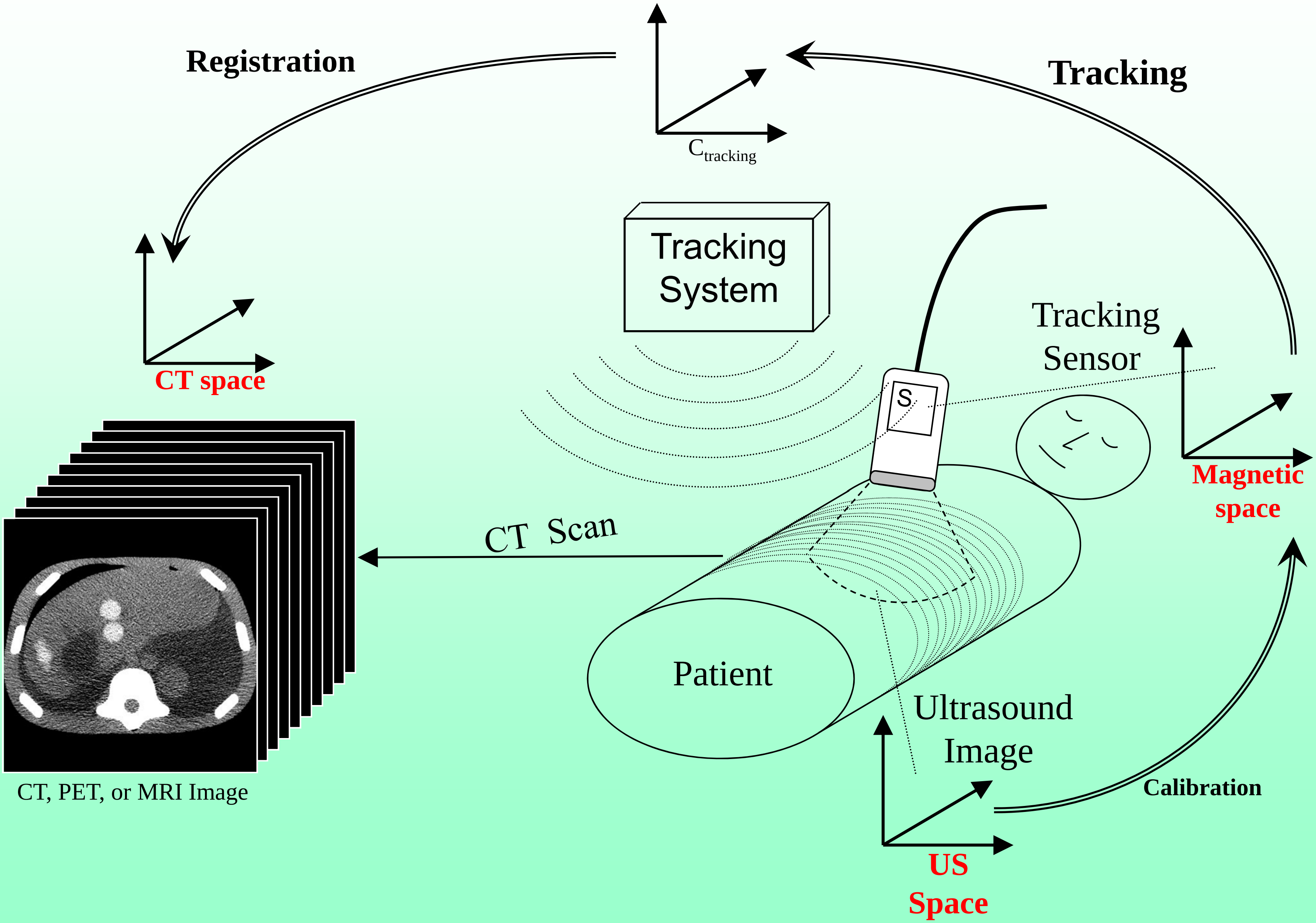
US and CT view, with planned composite ablation and tracked needle overlay

O.R. of the Future

- Navigation
- Visualization
- Automation
- Real-Time Fusion

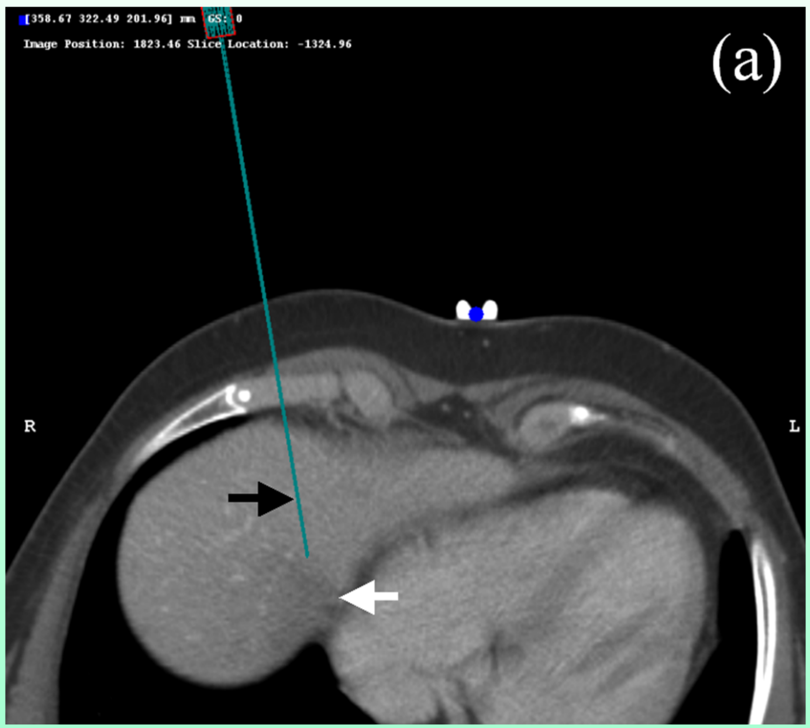


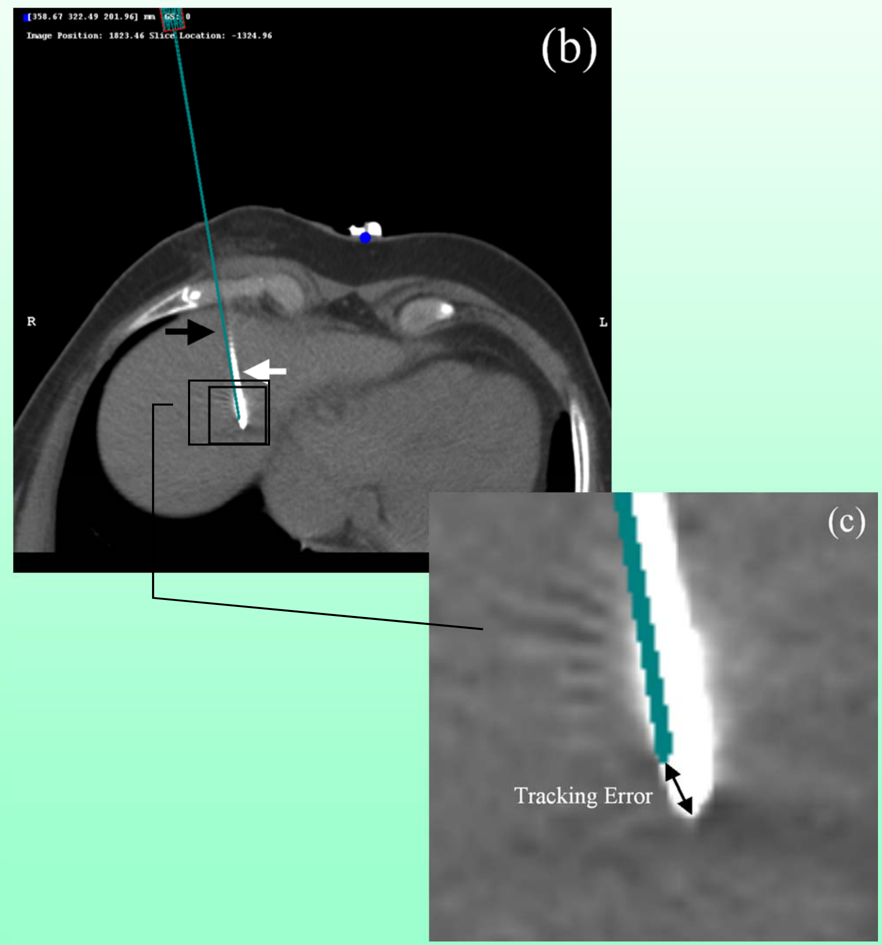
Medical GPS / Fusion IR



GPS-Tumor Ablation:

From Idea to Lab to Animal to Patient to FDA approval to Market

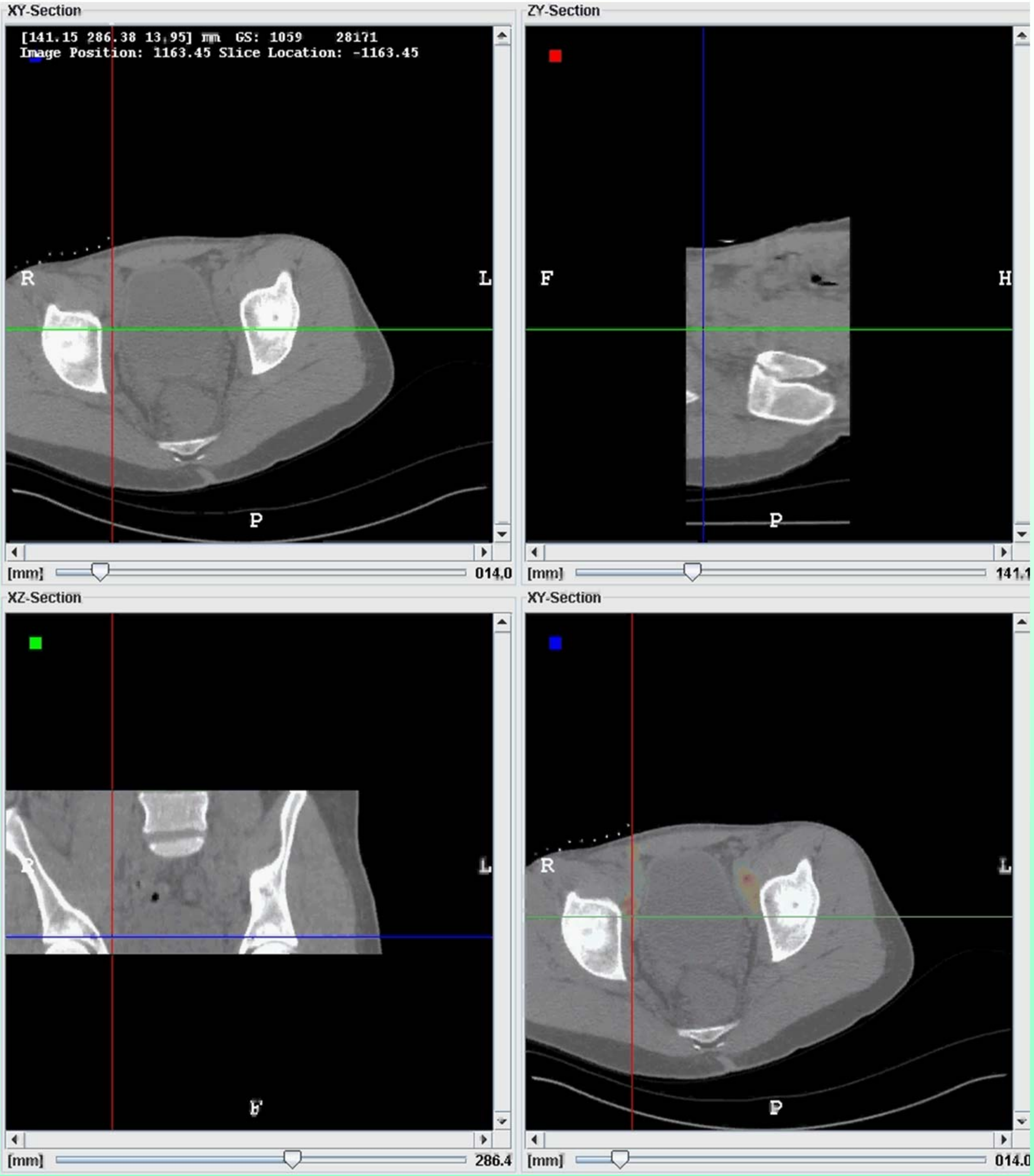




Black = Virtual Needle
White = Clandestine Cancer

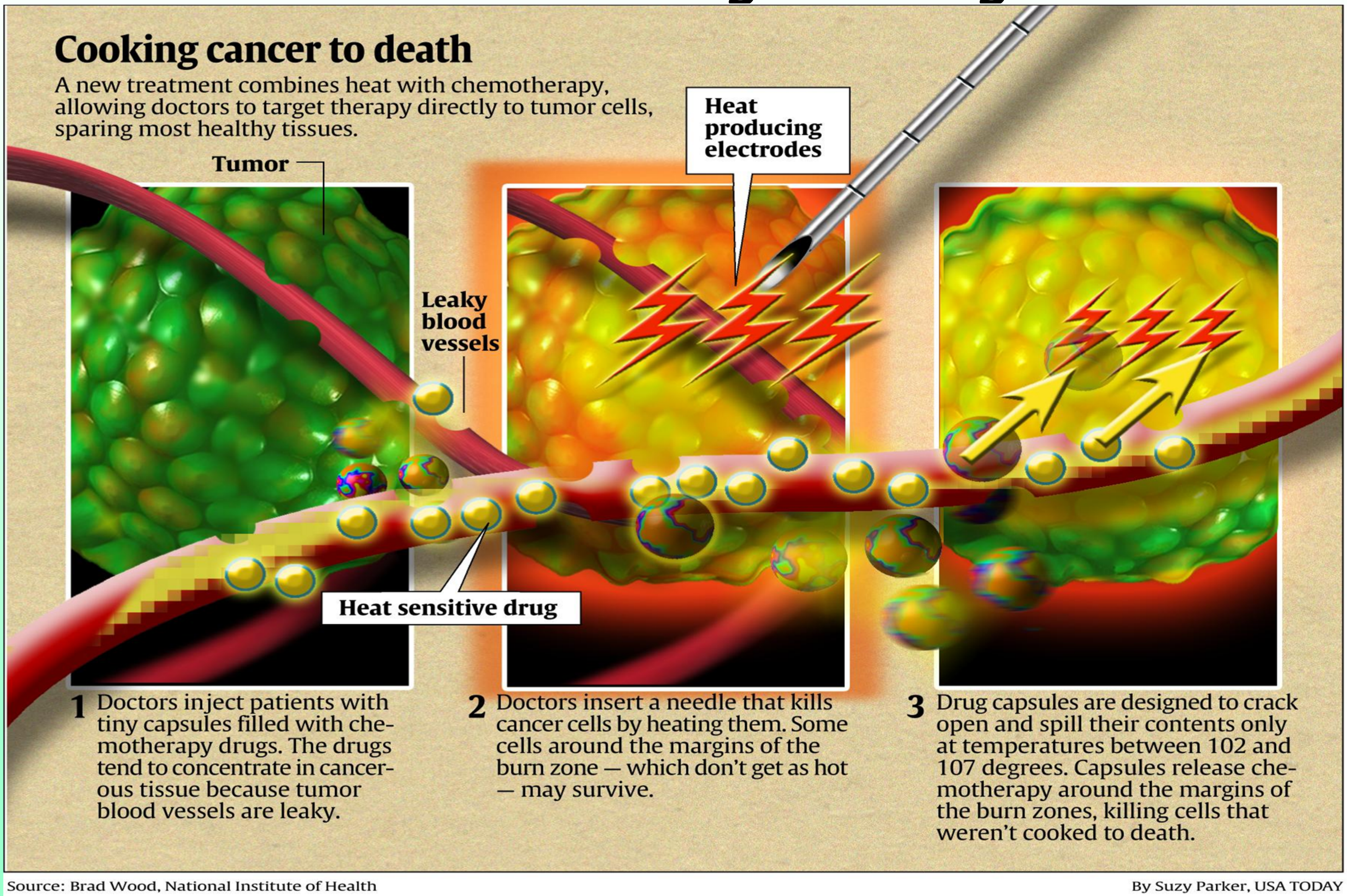
Accuracy, Error & benefit defined in >200 patient clinical trial

CT, US & PET guided fusion biopsy in patient with lymphoma



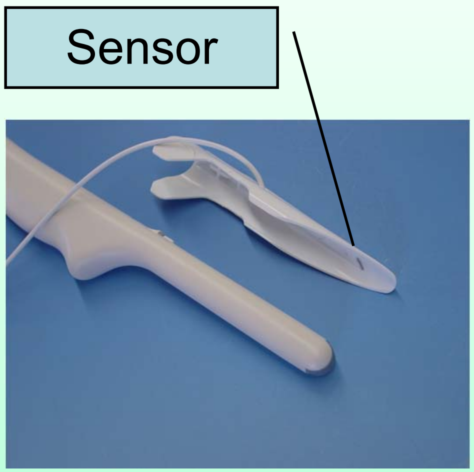
"Molecular Interventions"

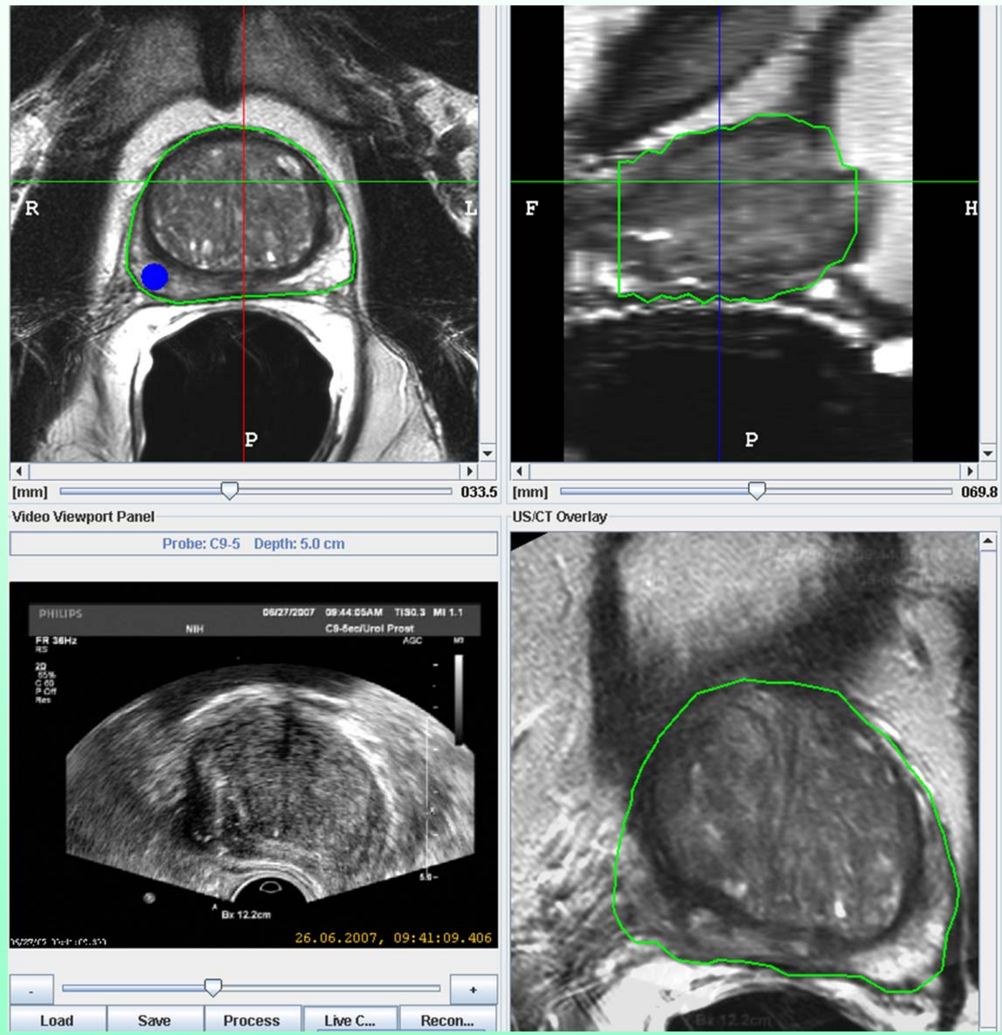
Device + Image + Drug



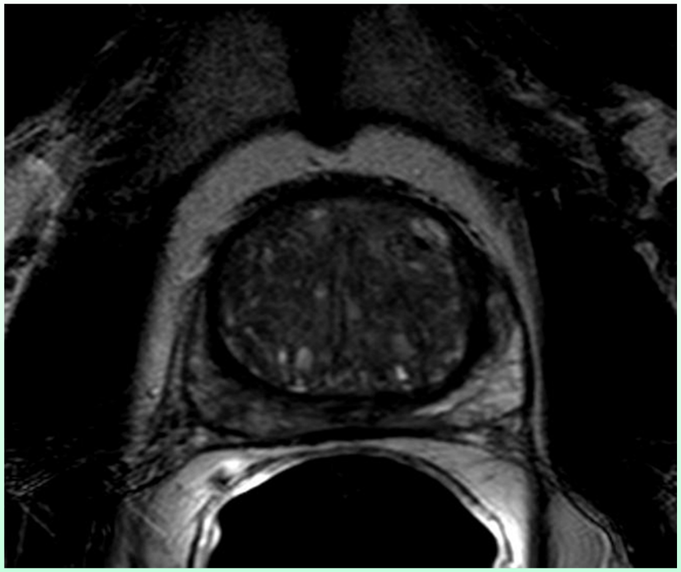
Prostate Interventions:

Idea to Design to Lab to Phantom to Animal to Patient

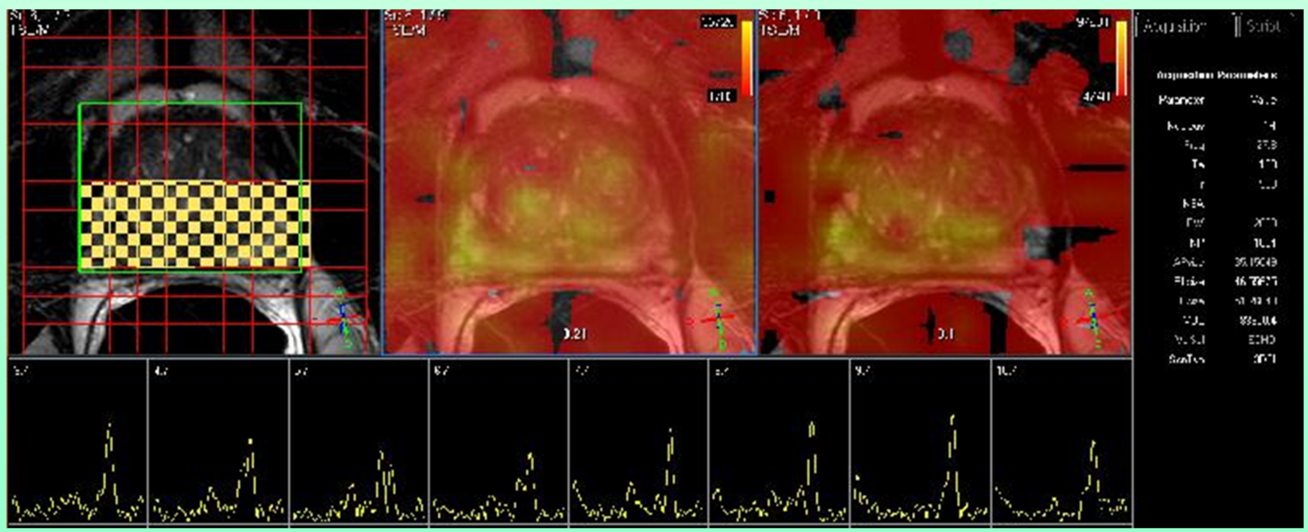




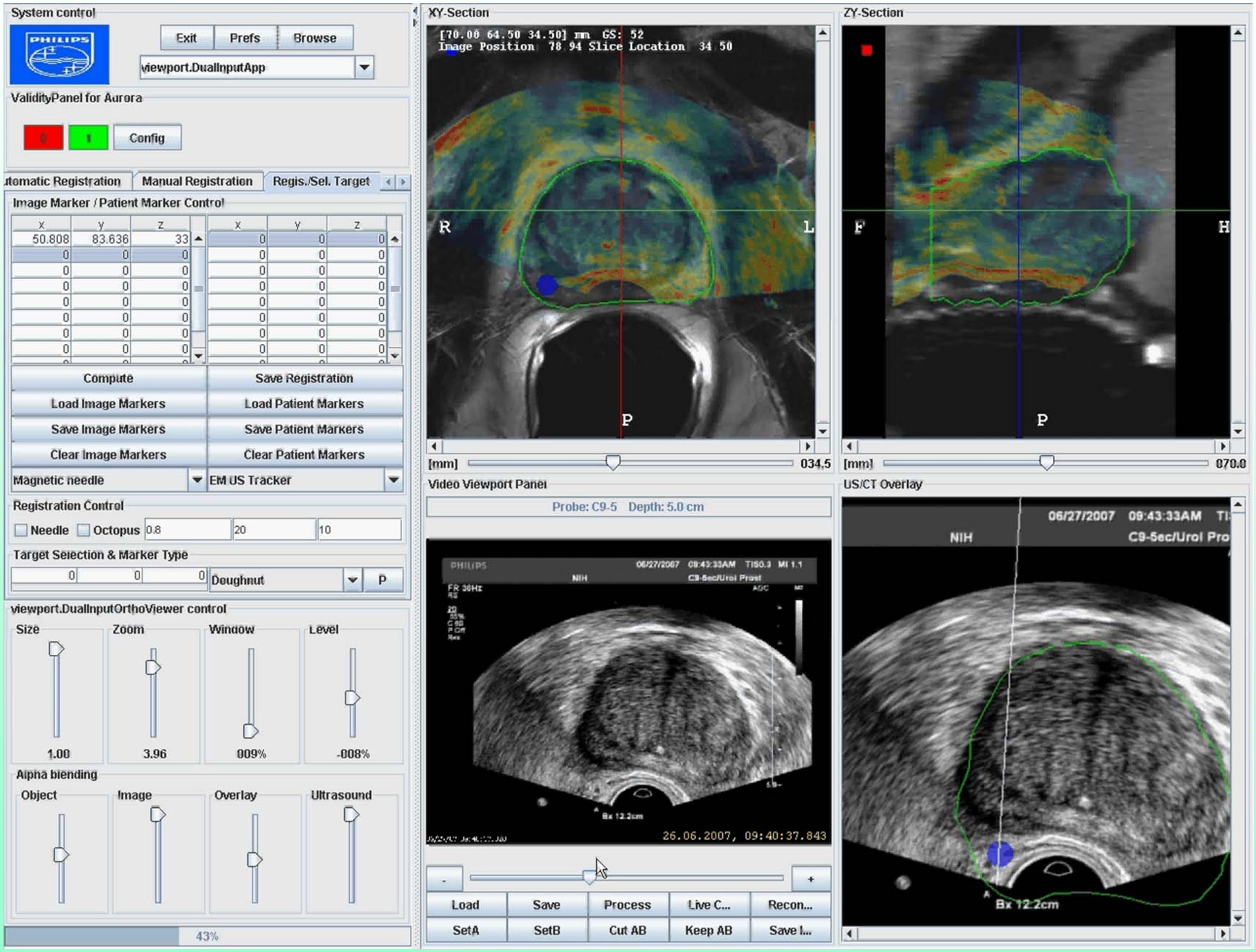
Smart Needles use MRI Info *outside* of MRI:



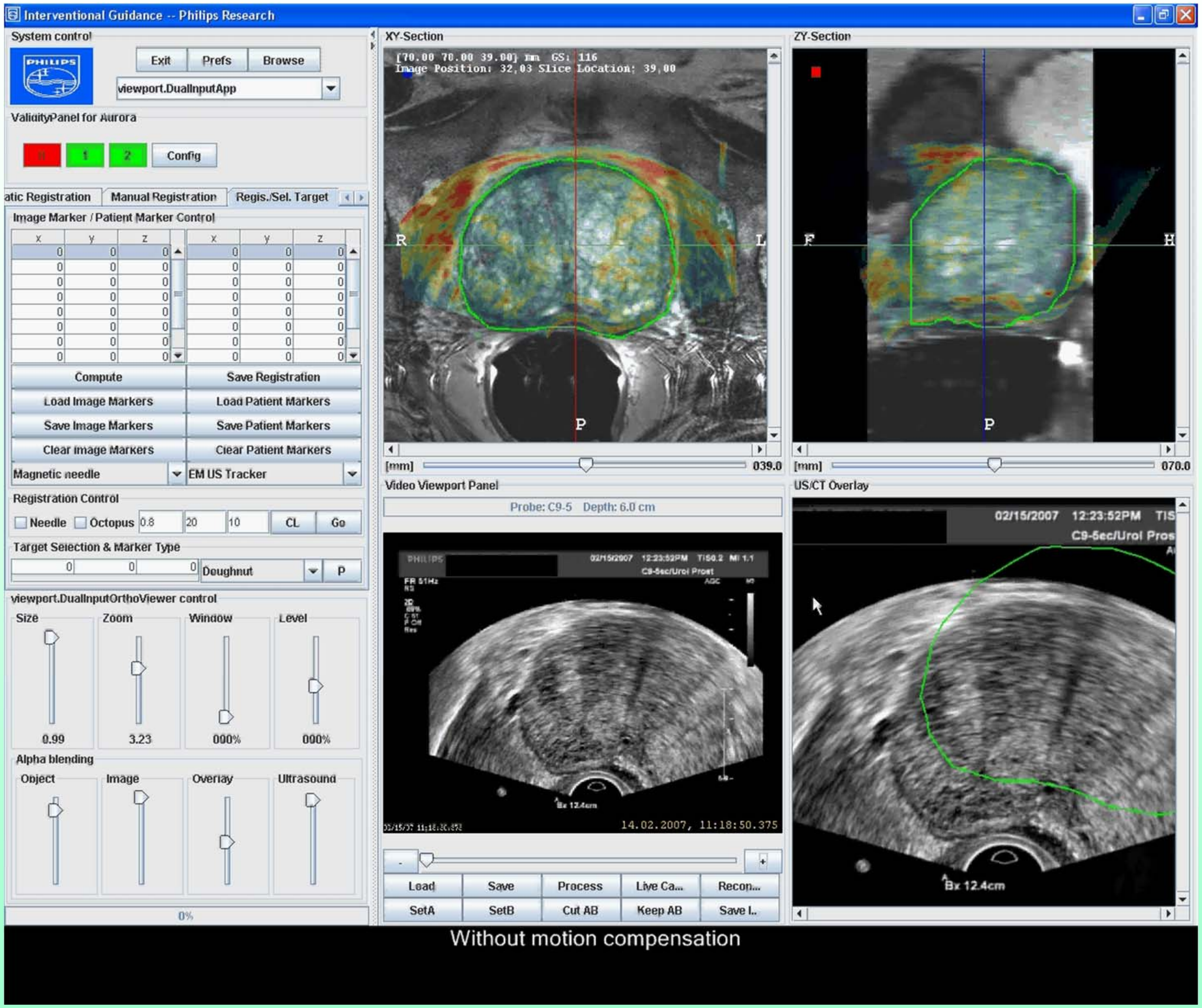
No need for MRI during procedure



GPS Fusion Makes the Dx



Automated Motion Correction

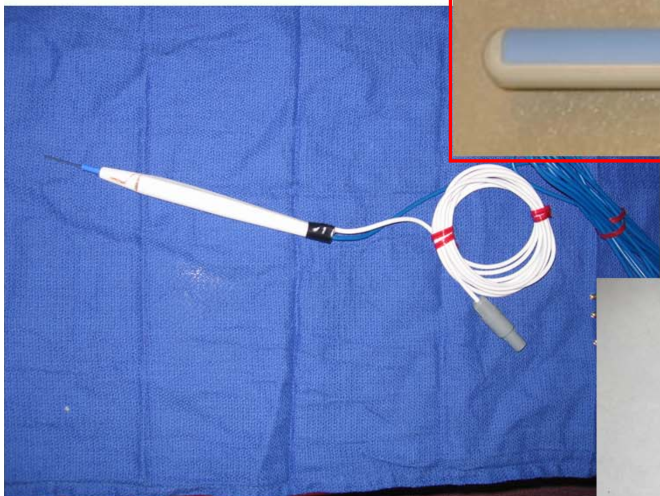


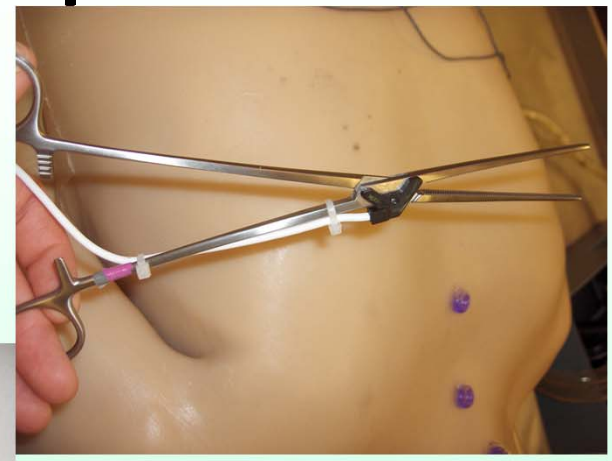
3.1 mm error

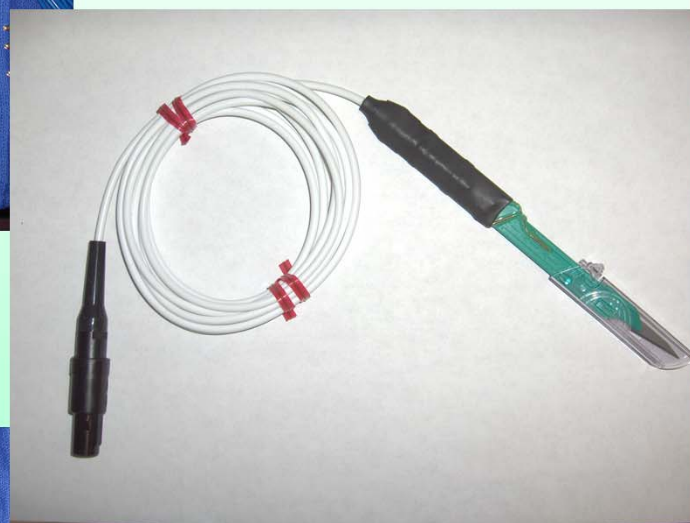
>140 patient trial

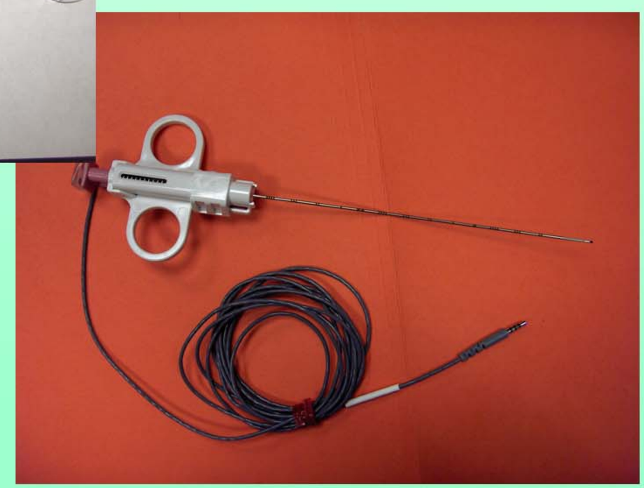
83% pts w high suspicion MR had positive fusion bx
Aggressiveness correlated with imaging

Smart Surgical Equipment

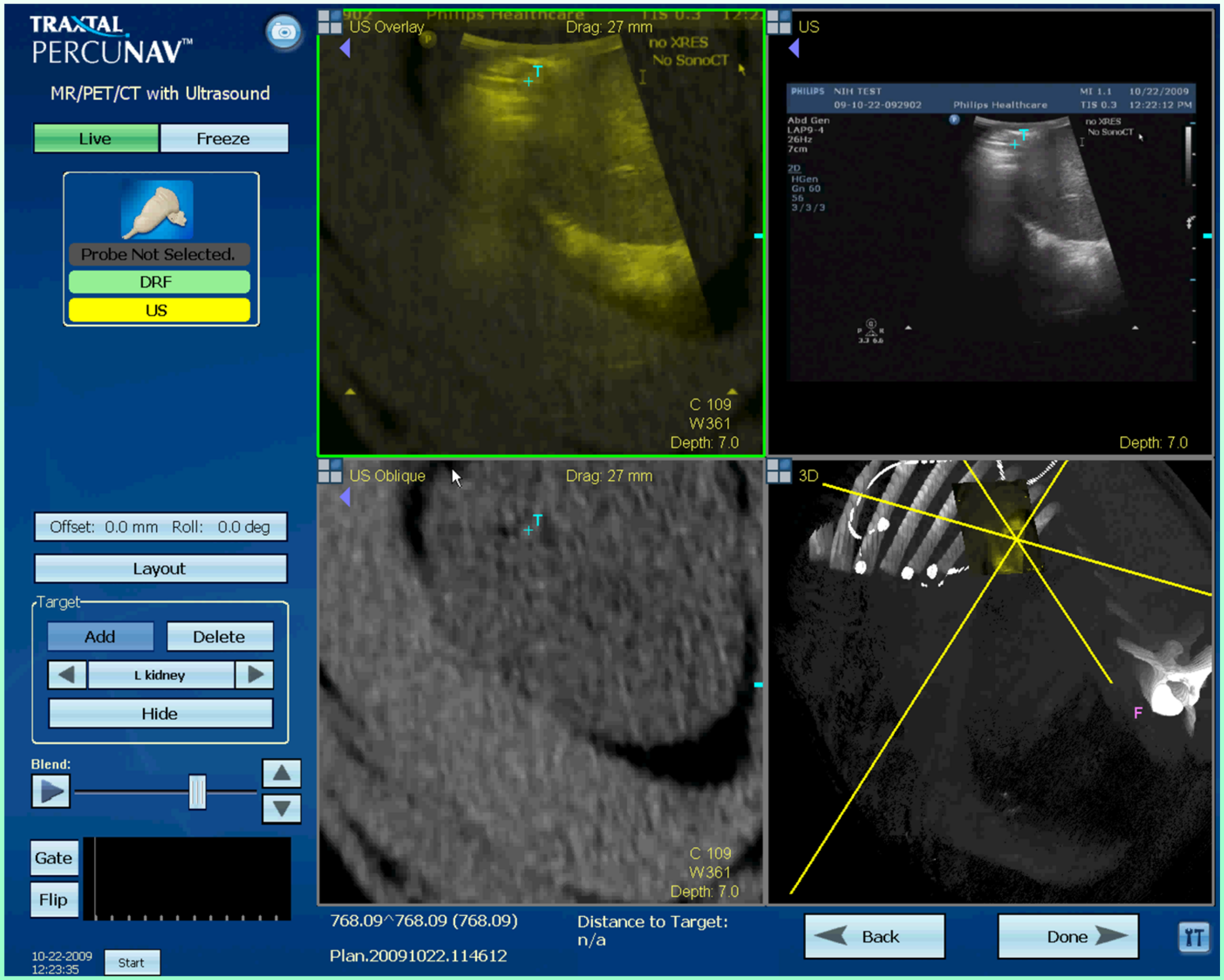




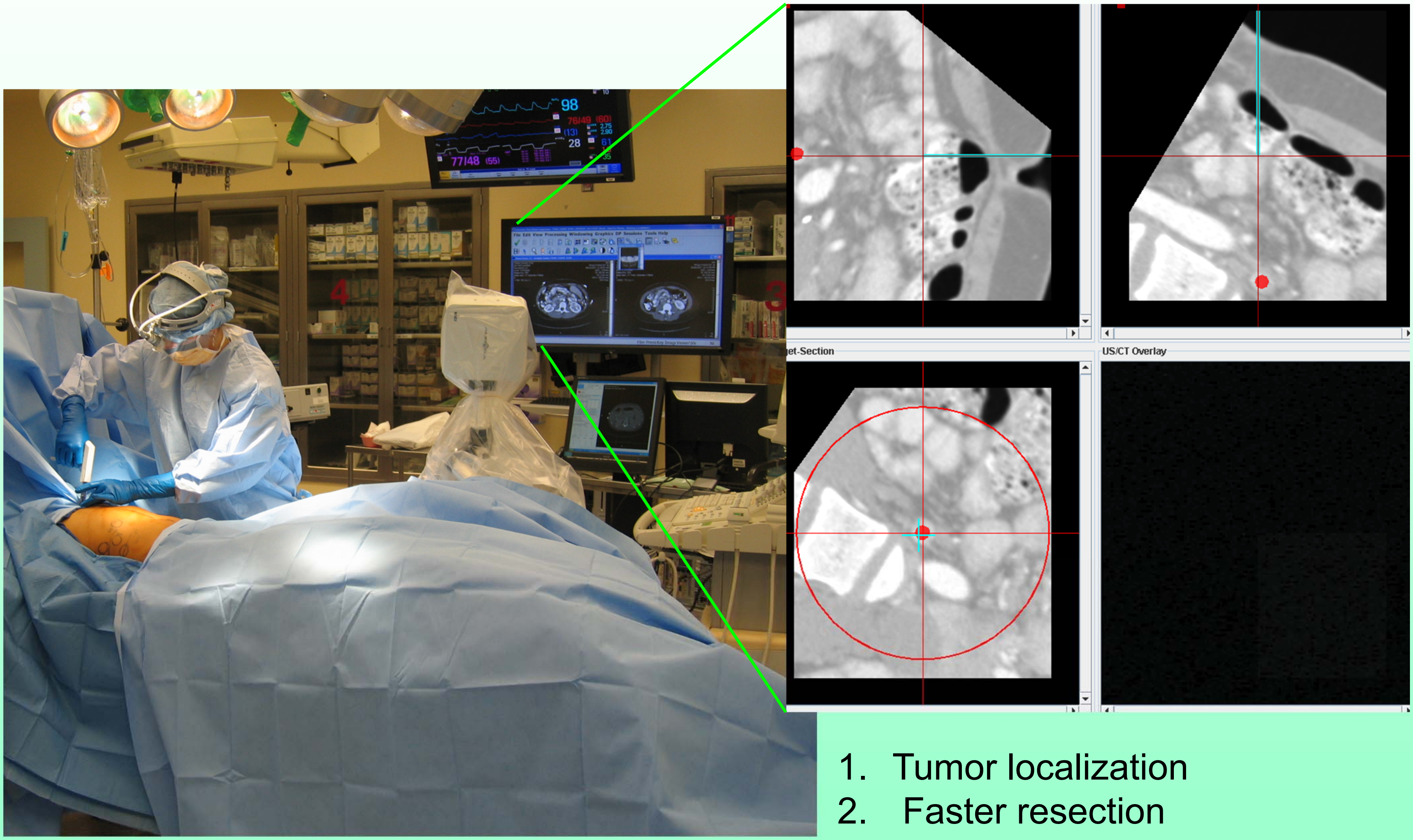




Multi-Modality Surgery

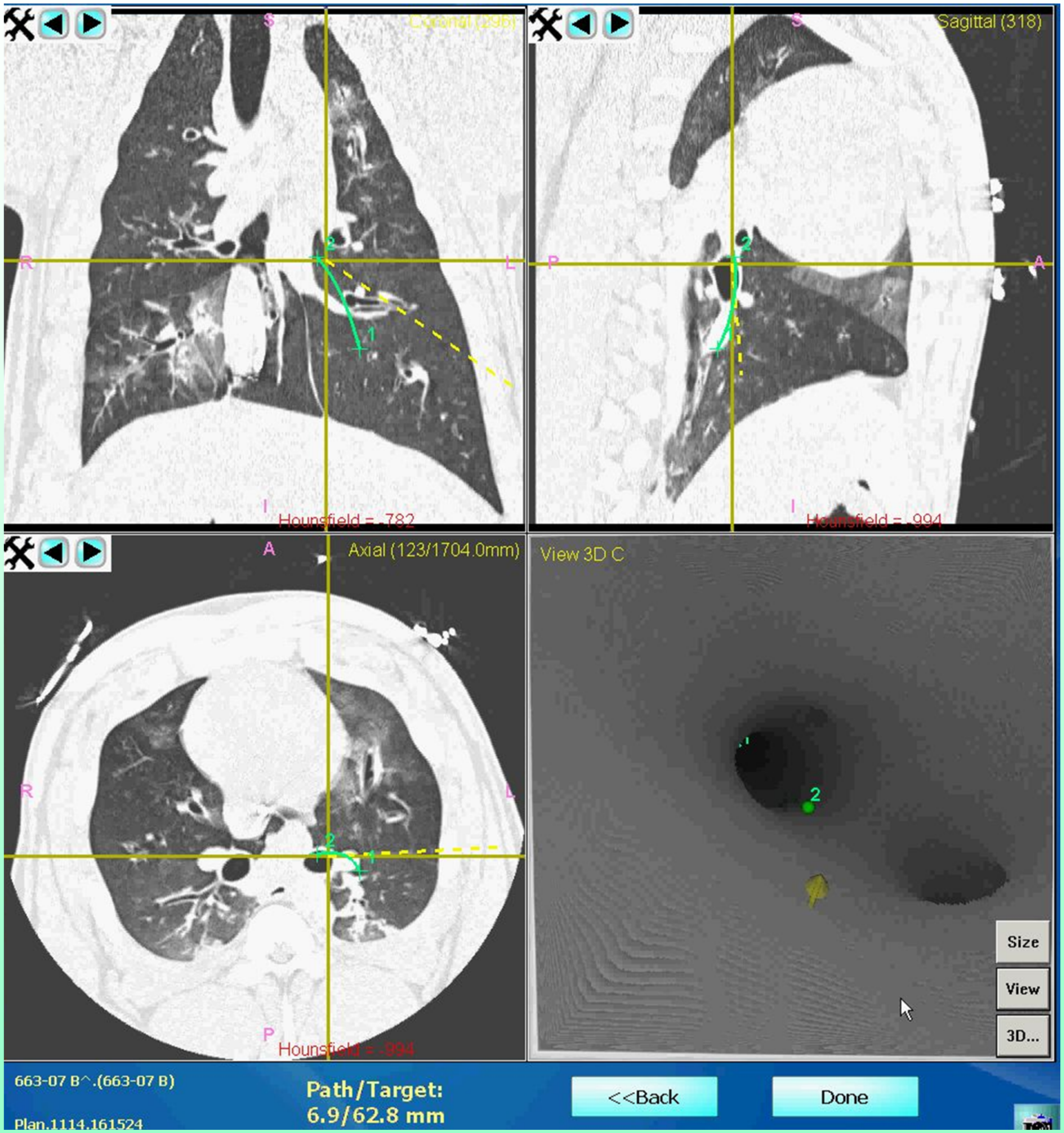


Smart Surgery



1. Tumor localization
2. Faster resection

Steerable Bronchoscopy Catheter



Tracked Stent Grafts for Aortic Aneurysm Repair

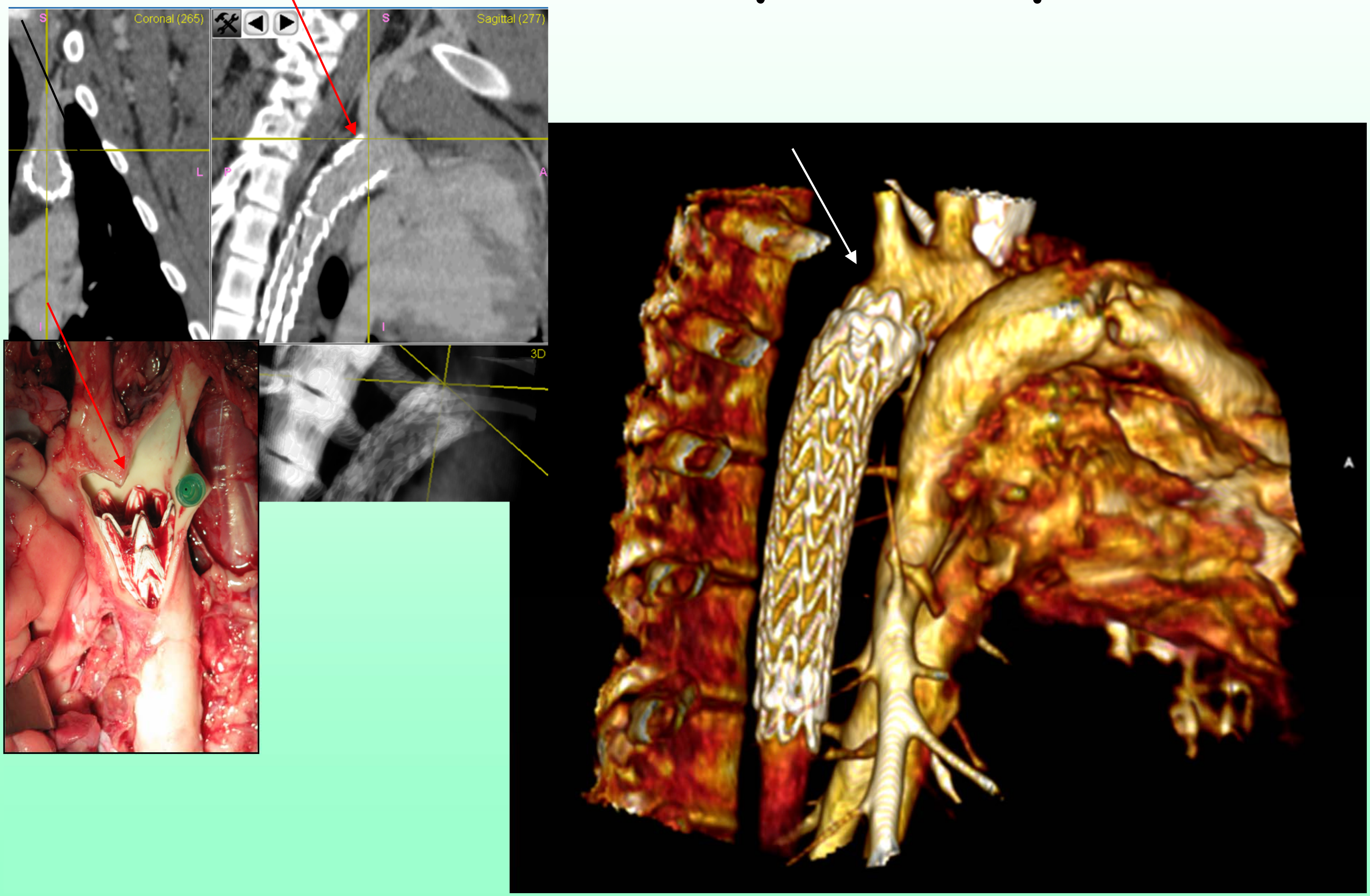


Image to Tissue Correlation for Personalized Oncology & Drug Discovery

Imaging

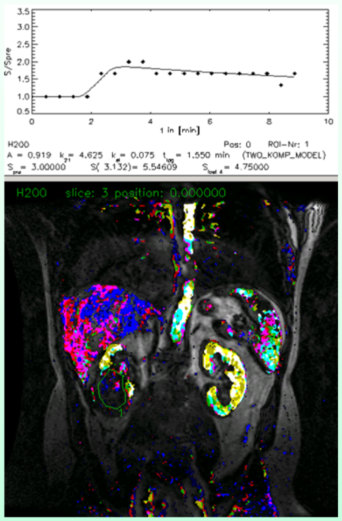
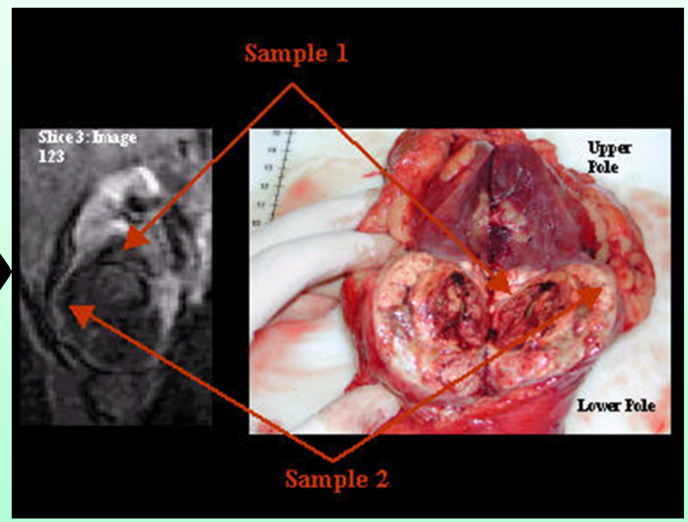
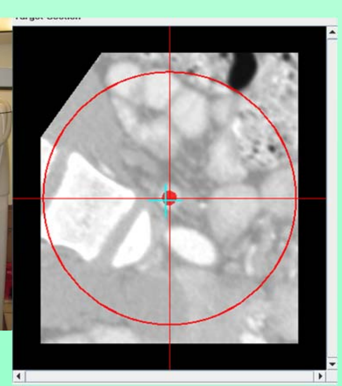


Image registration

Sample collection

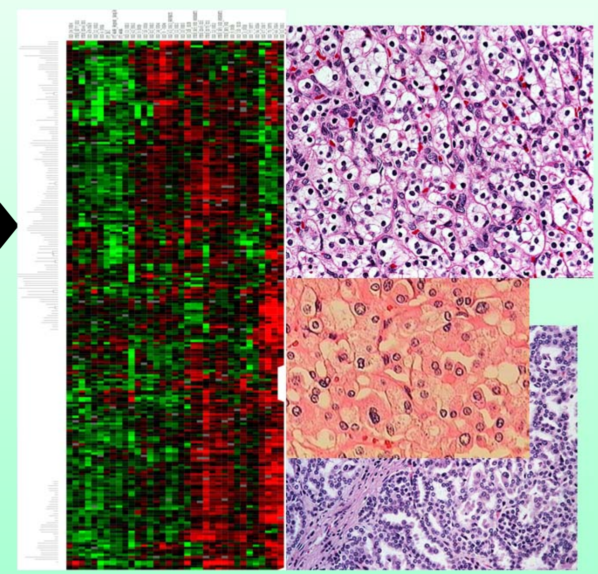




Biomarker

Gene

Protein

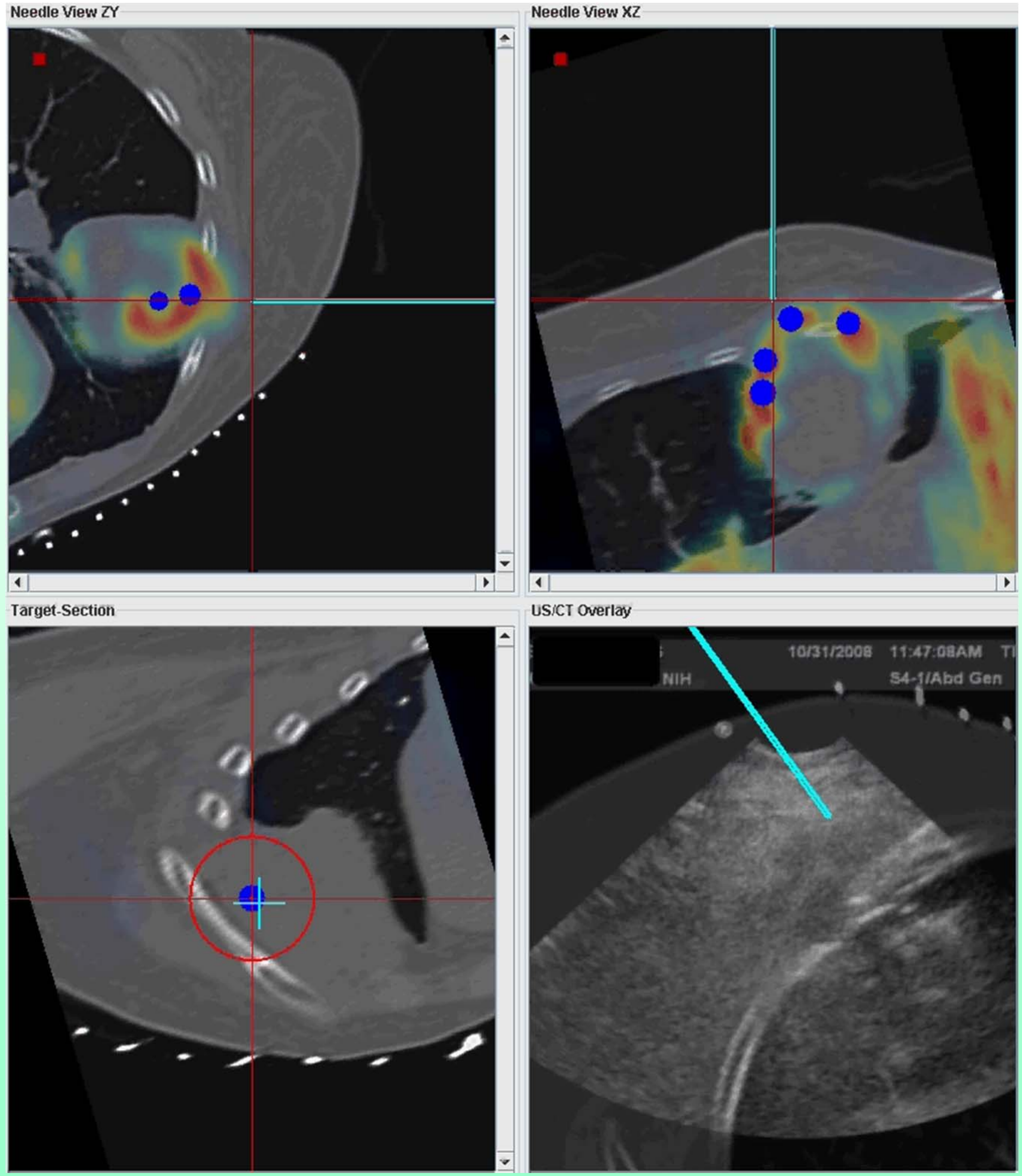


prognosis
response
sensitivity
resistance
metabolism

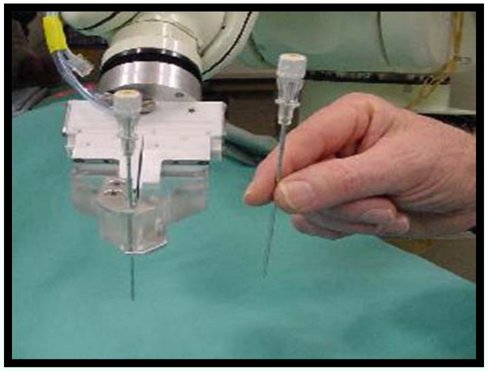
Image to Tissue Correlation for Personalized Oncology & Drug Discovery

- Biomarkers
  - Identify target
  - Verify delivery
  - Predict response
  - Toxicity
  - Prognosis
- Individualize tx / Pt-specific cocktails
  - Timing
  - Sensitivity
  - Resistance
- Drug Discovery
  - Target
  - Efficacy

PET Guided Interventions

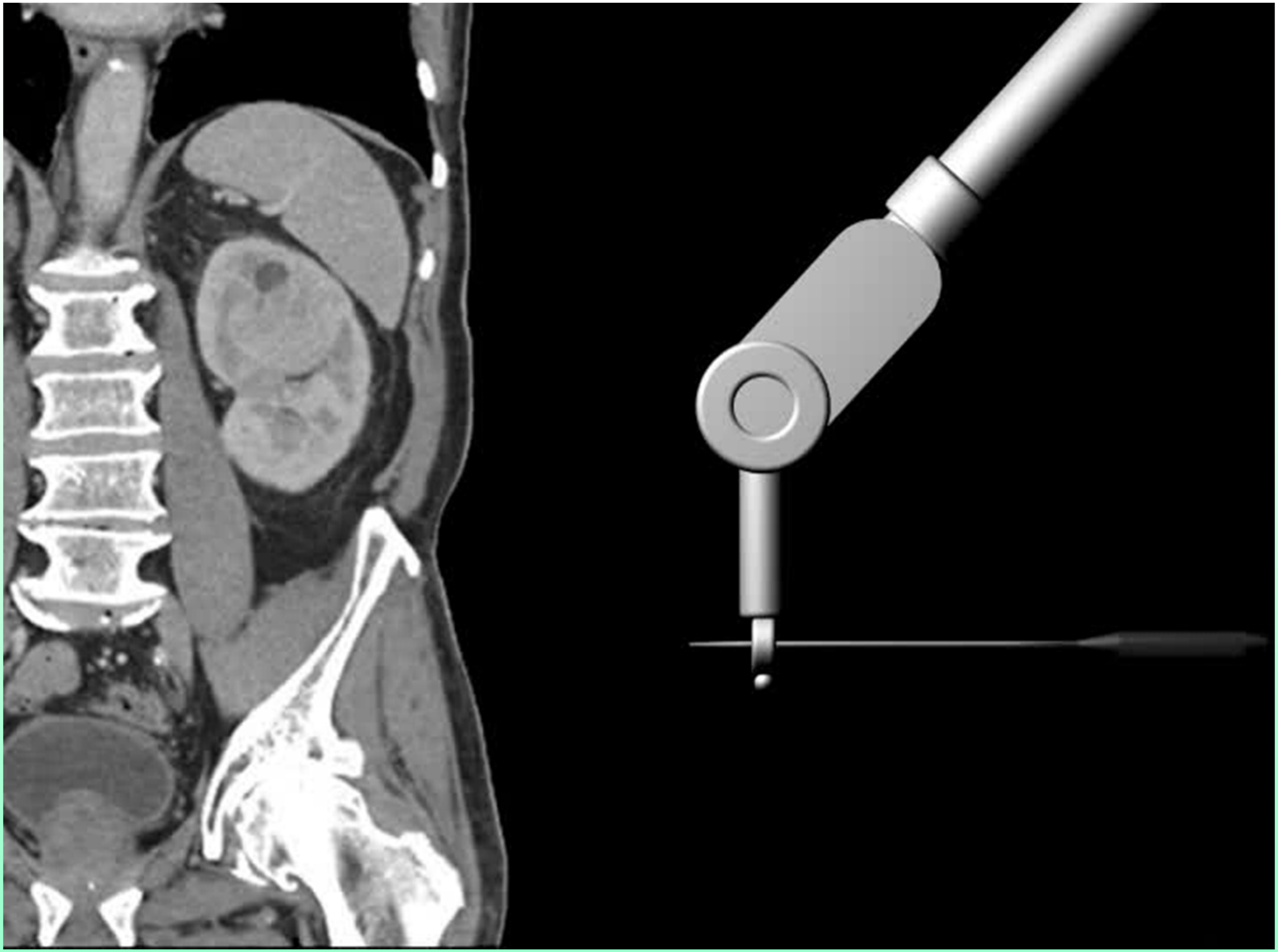


Robots in IR



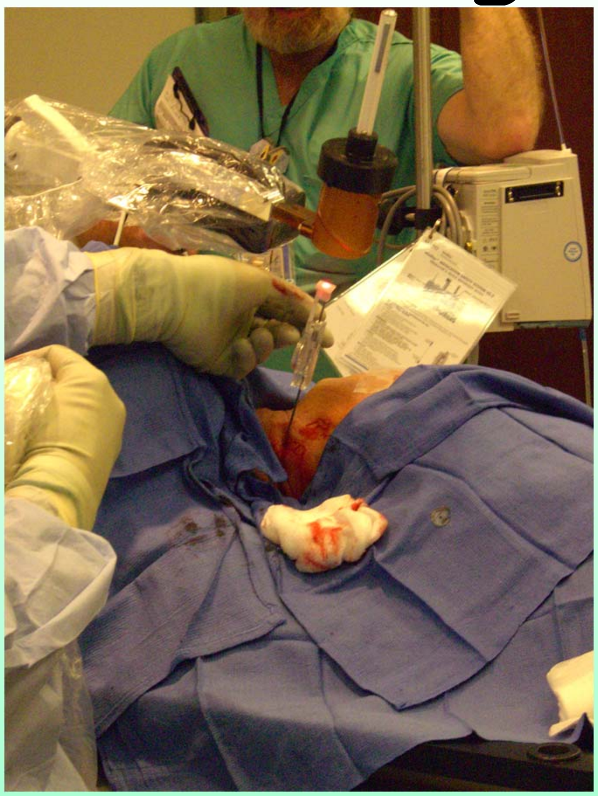
- Accuracy
- Less radiation
- Fast, Cost-effective
- Efficient
- Fewer needle attempts
- Tx planning
- Consistency

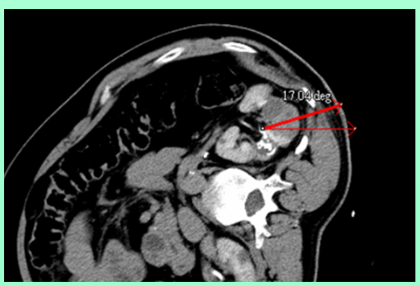
= Better Outcomes

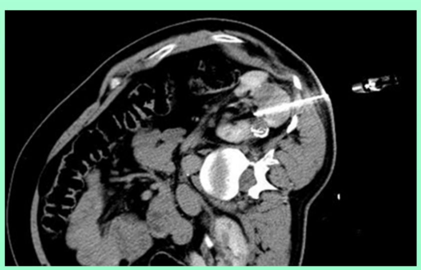


Bill Charboneau, Mayo

Integration of Robotics & CT-guided Ablation

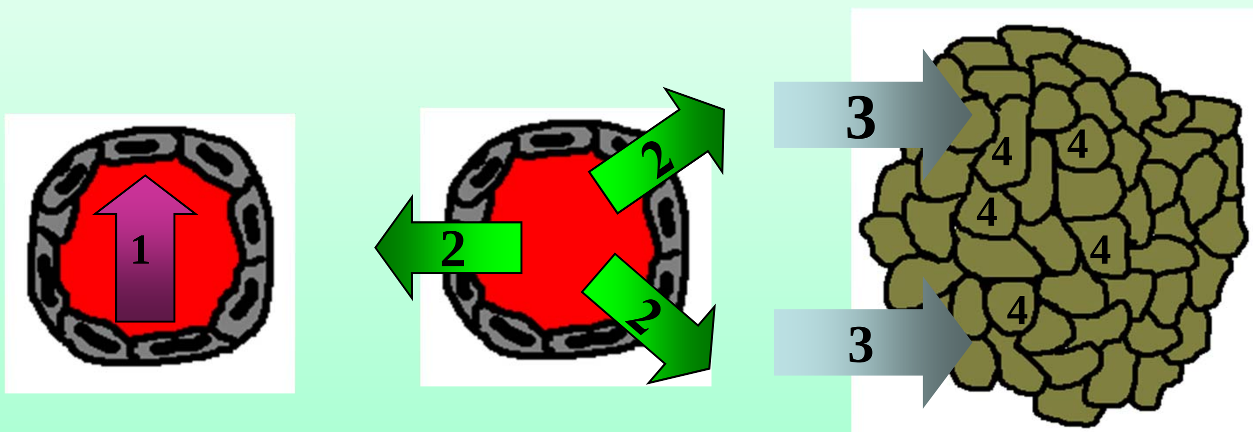




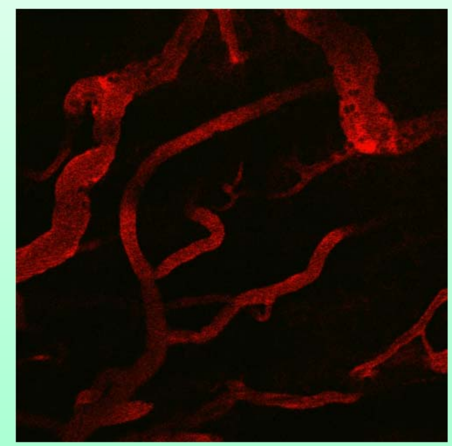


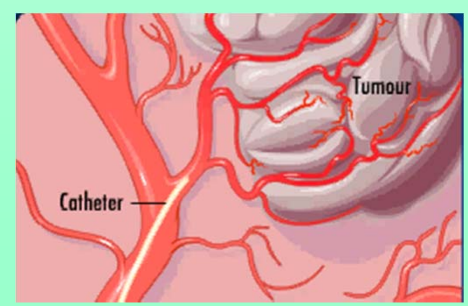
Drug Delivery Barriers

1) IV vs IA
2) Vessel wall
3) Interstitium
4) Cell membrane & staying in cell (nucleus)



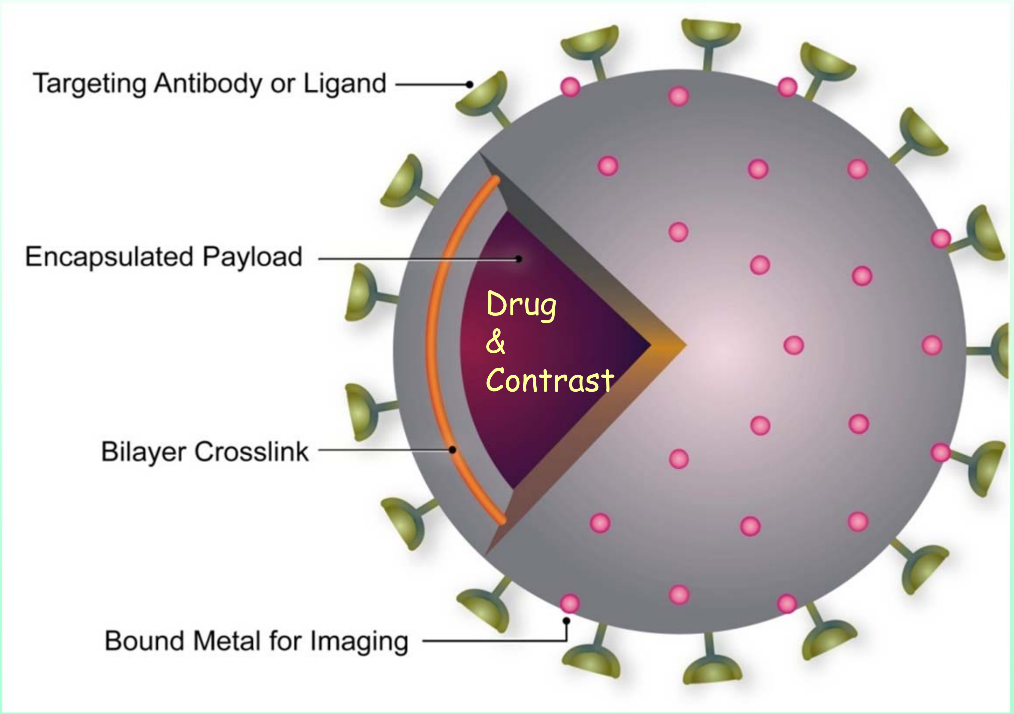
Blood vessels
3.3 kDa Dextran



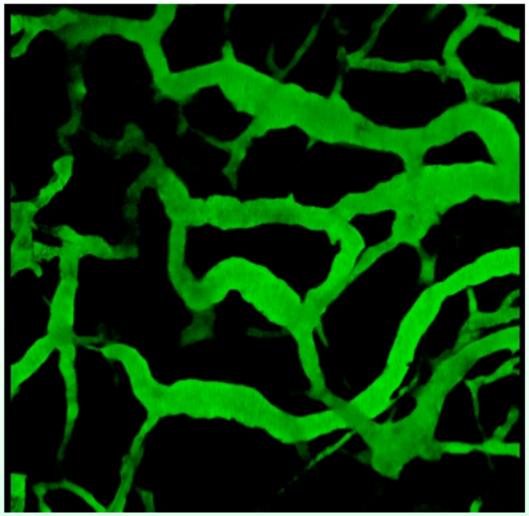


Molecular Interventions:

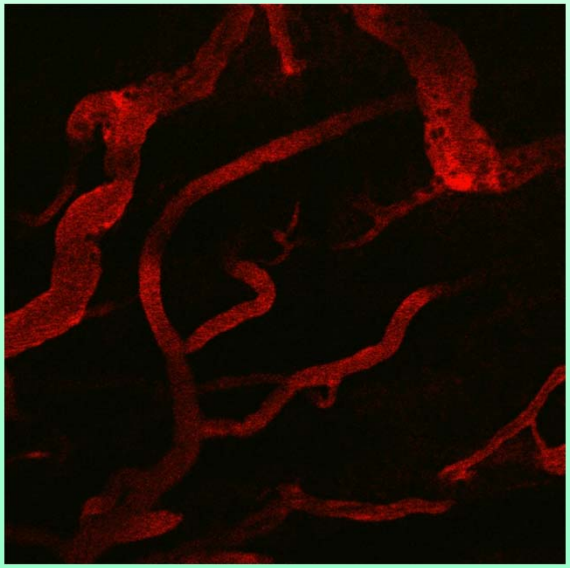
targeted drug designed for device



50-100 nm

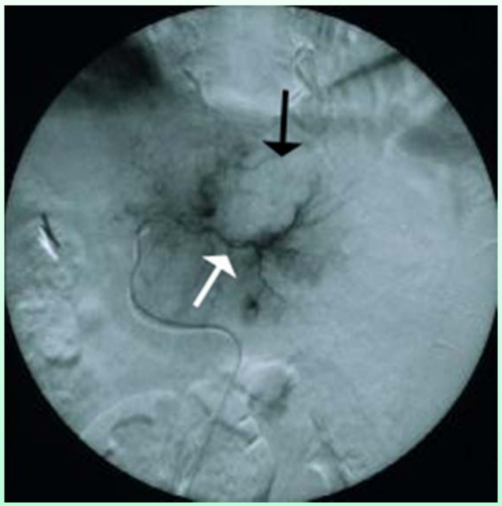


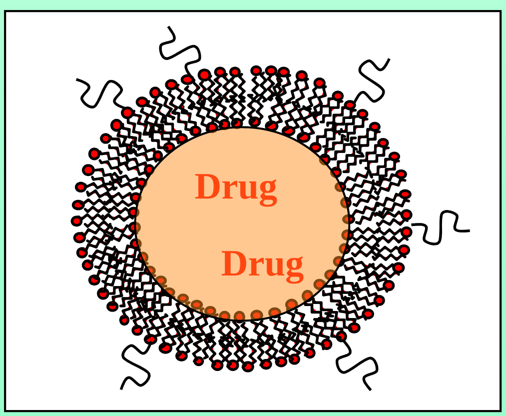
Tumor vasculature
ideal size for nanomedicine

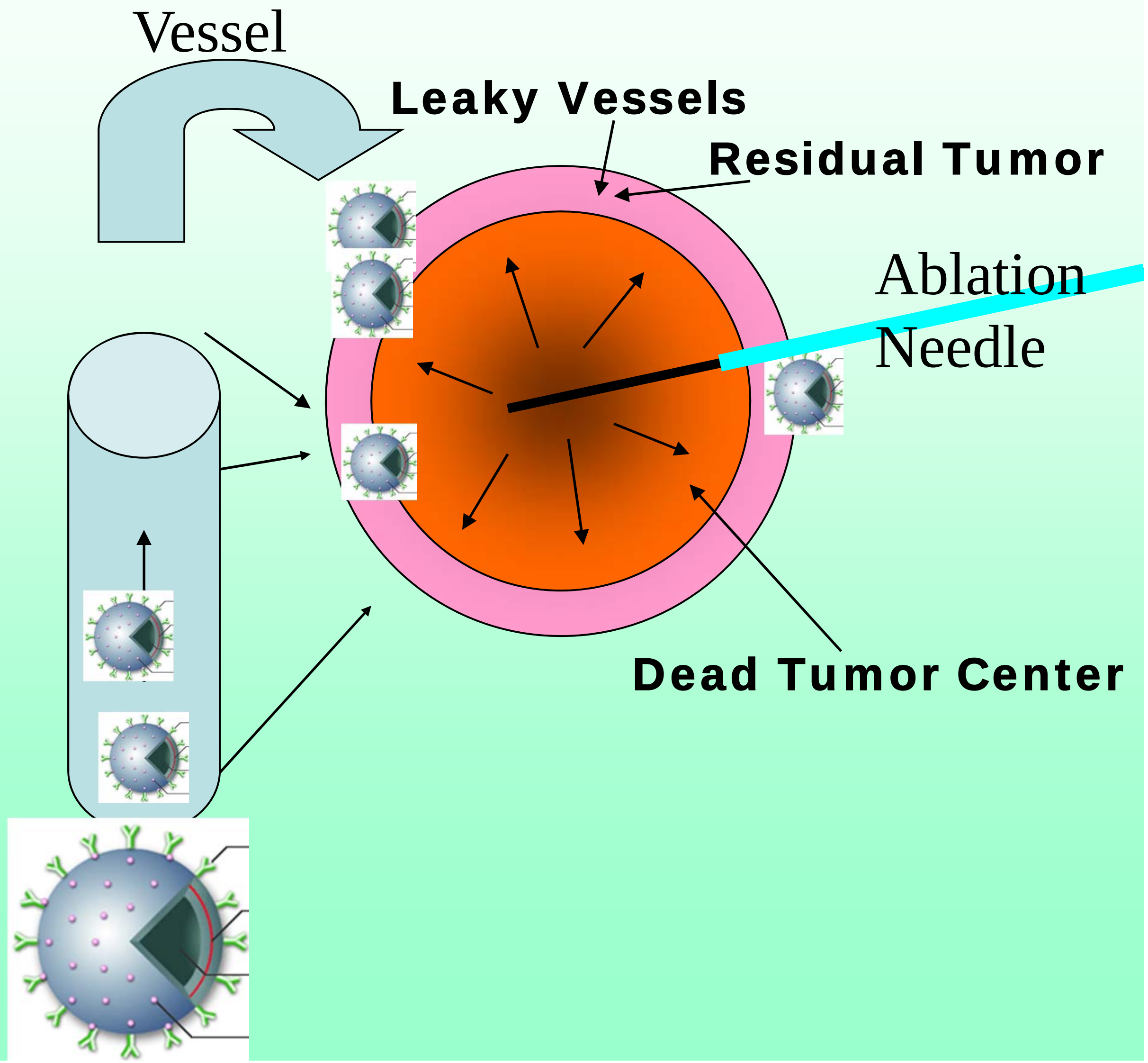


Combination Targeting:
Smart IV Drug + Thermal Needle Device

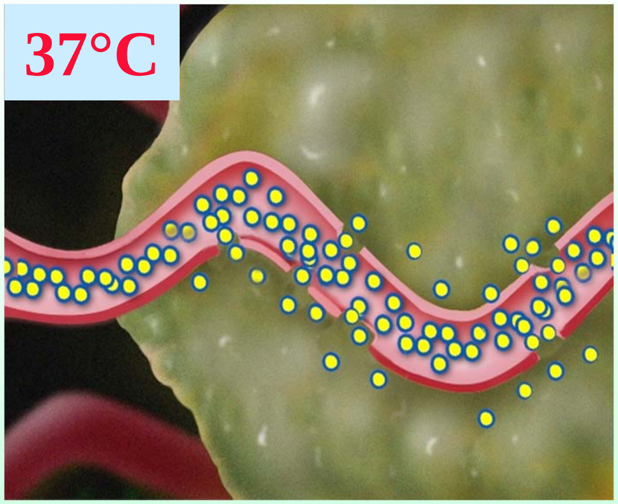
Extravasation @
Edge of RFA



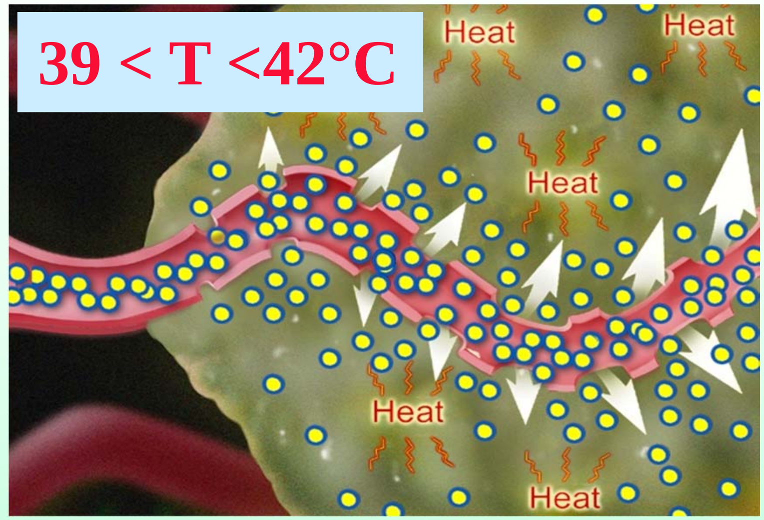




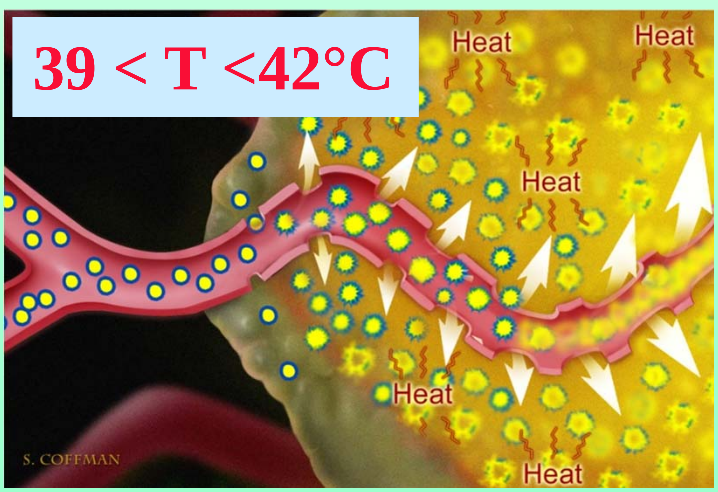
Physiologic, Thermal, & Chemical Synergy



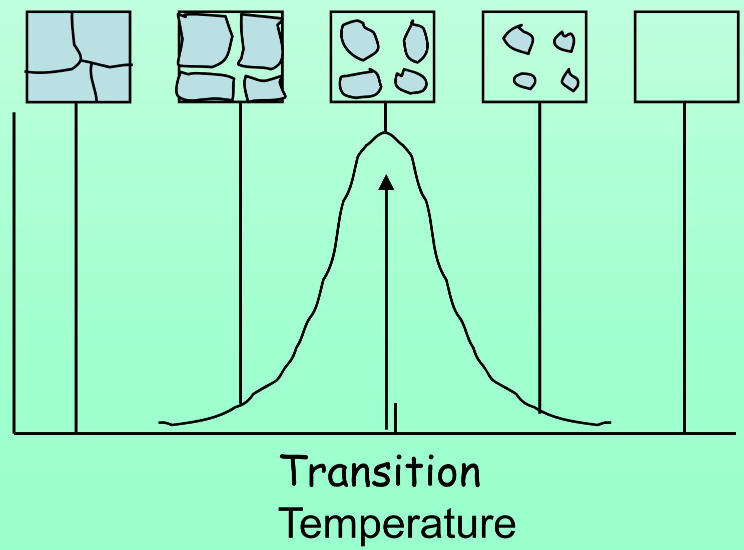
Leaky tumor vessels



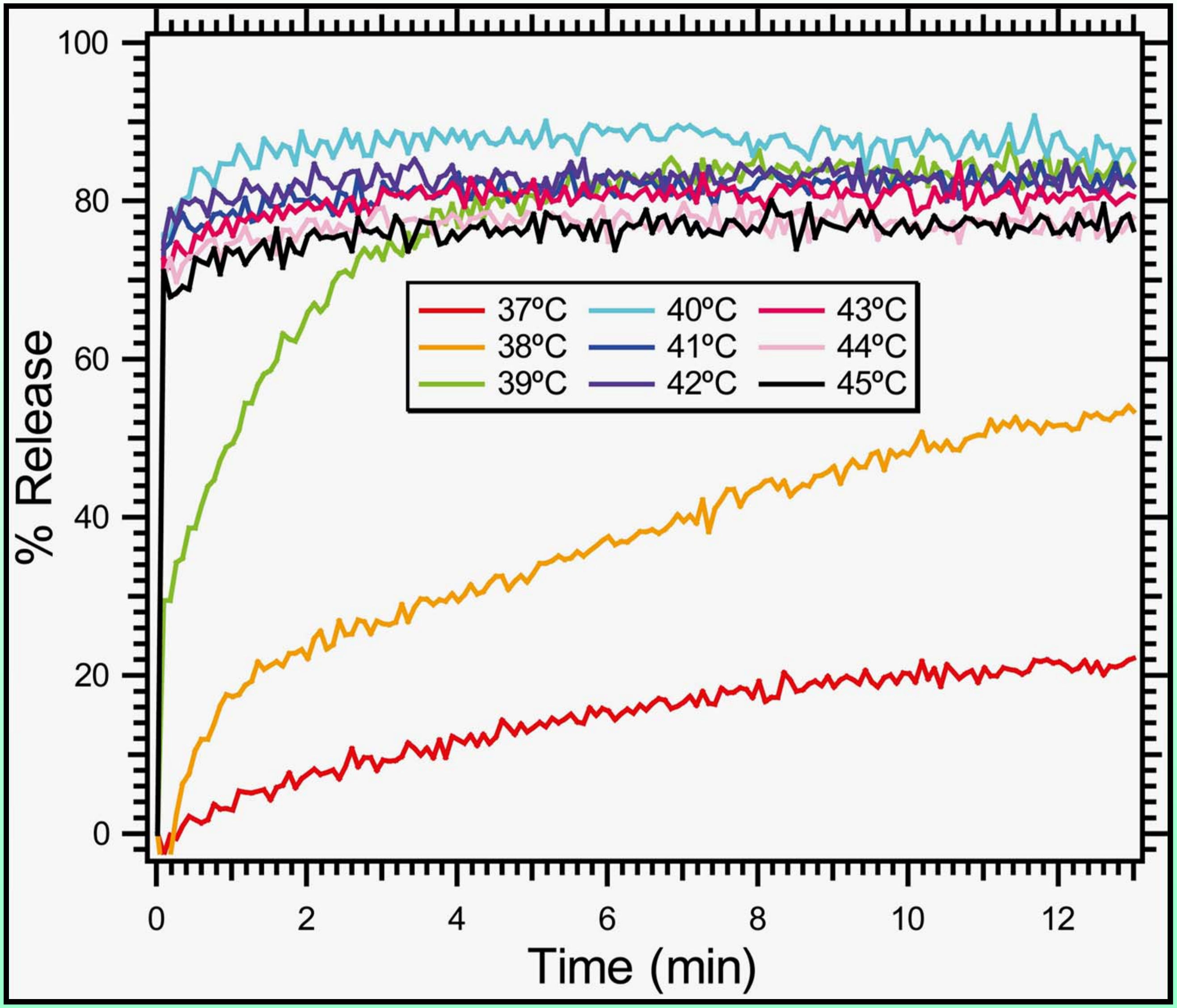
Heat alters permeability



Cargo deployed @ 39-42 deg

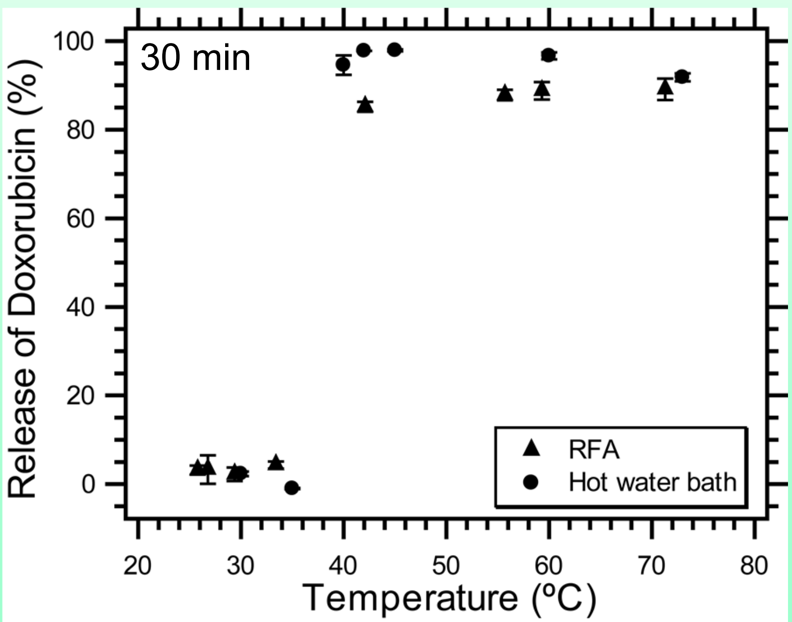


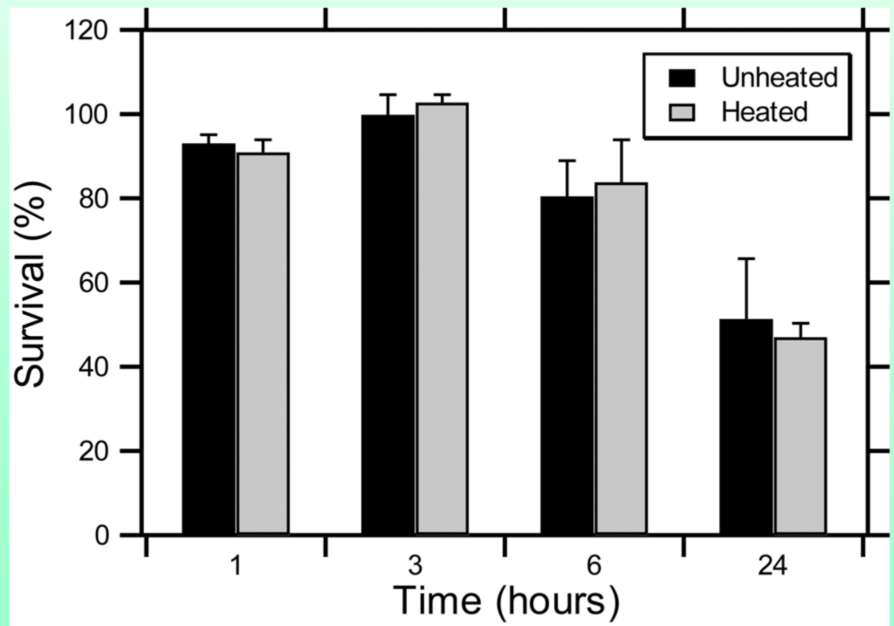
Percent drug release in plasma over time at diff temperatures



RFA and ThermoDox: in vitro feasibility

- Drug Release Independent of Heat Source
- Equivalent Cytotoxicity After Heat

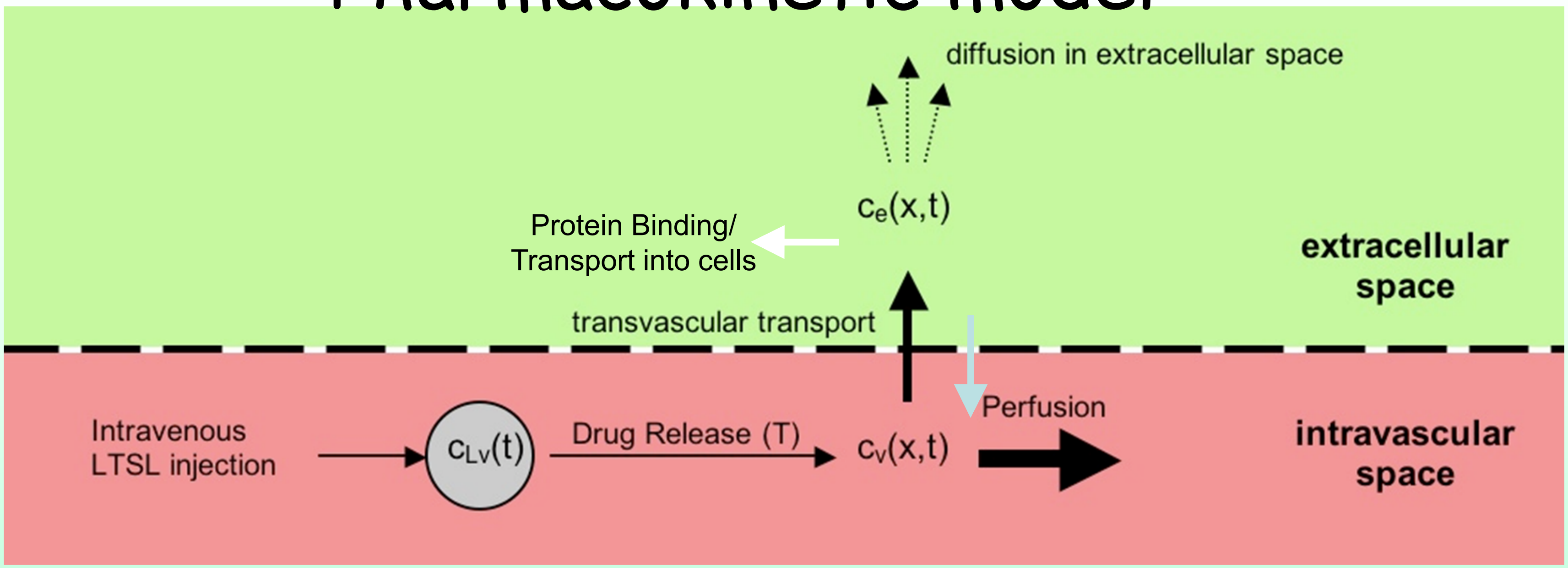




JC Adenocarcinoma cells

Dox heated for 12 min, $P > 0.05$

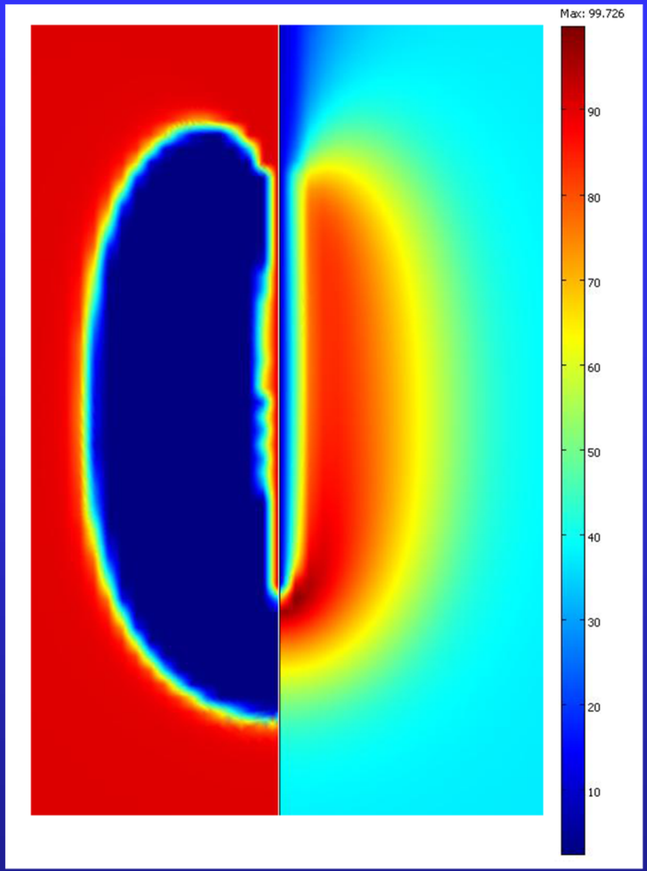
Paired heat transfer & Pharmacokinetic model



Transvascular Transport depends on:

- Vessel Permeability
  (depends on drug molecule, f(T))
- Vessel Surface Area
- Perfusion (f(T))

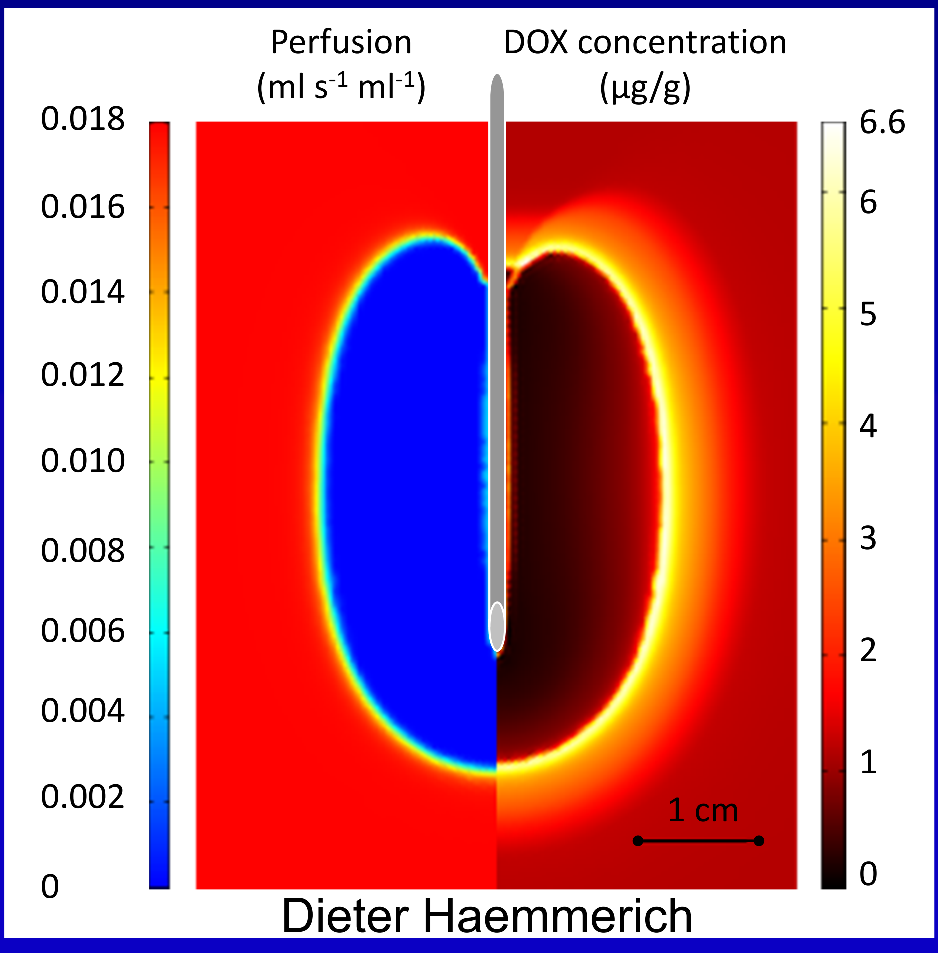
Modeling Perfusion vs Temp

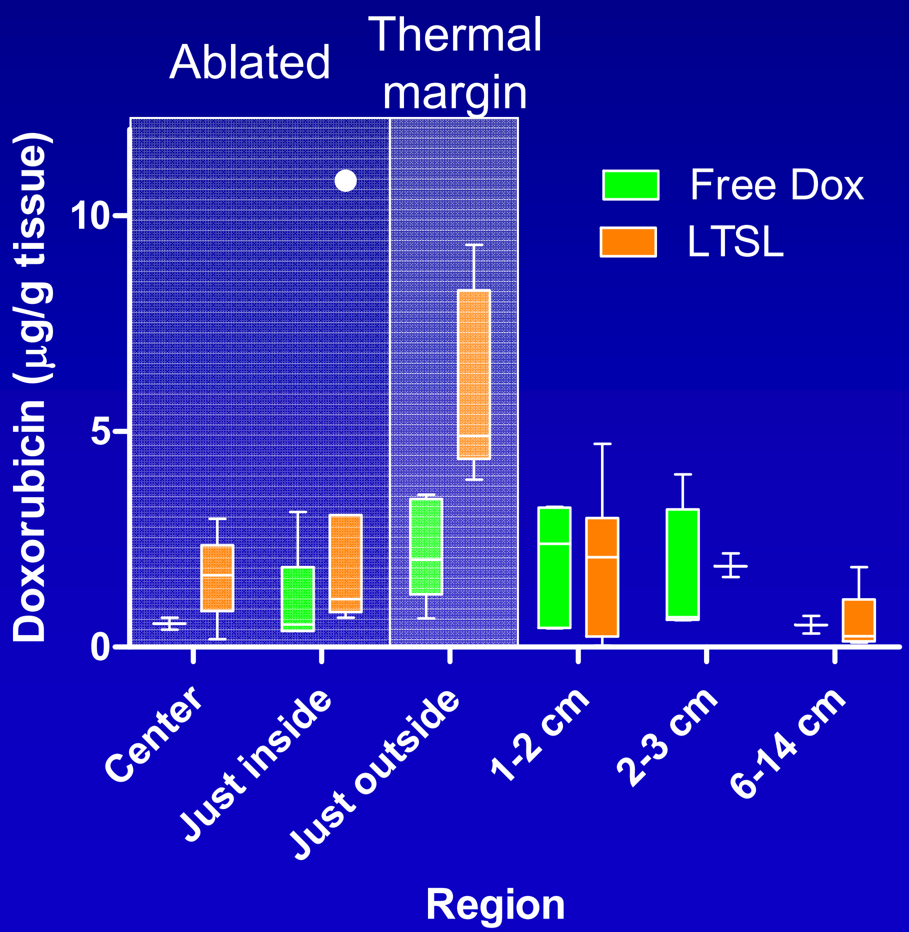


Perfusion (%)   Temperature

RF ablation:
Comparison Free DOX & LTSL

- Increased drug delivery to thermal margin

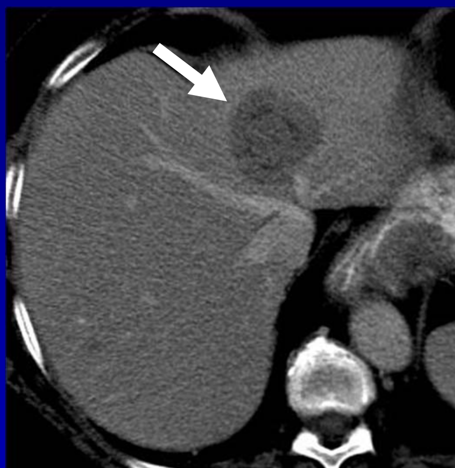




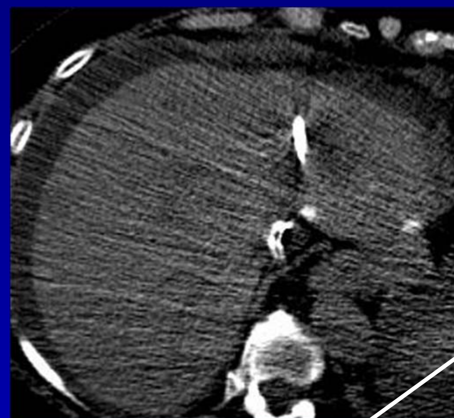
Imaging Drug Effects:

ThermoDox + RFA:
Idea, animal studies & Phase I @ NIH
Phase III: 5 countries, 40 cancer centers

Pre-procedure

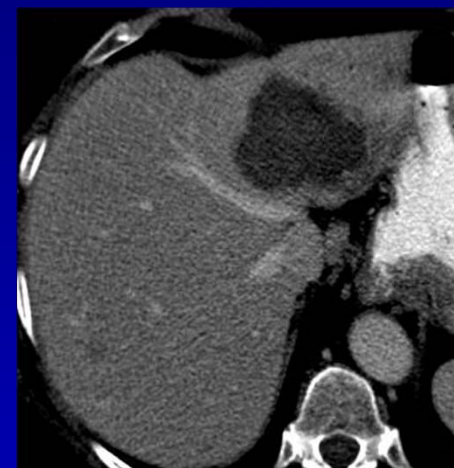


Intra-procedure

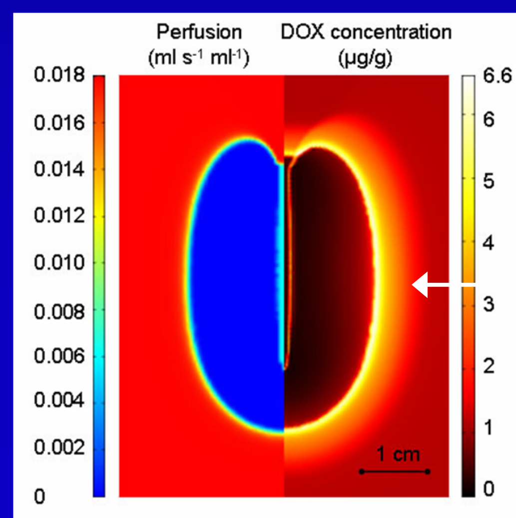


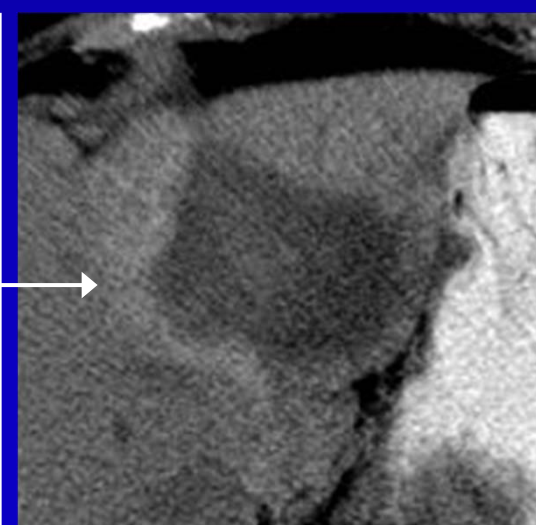
Day 71

12 month



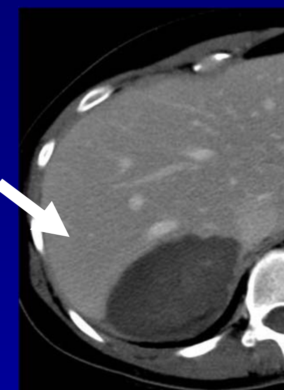
- Enhancing rim corresponds to predicted drug location

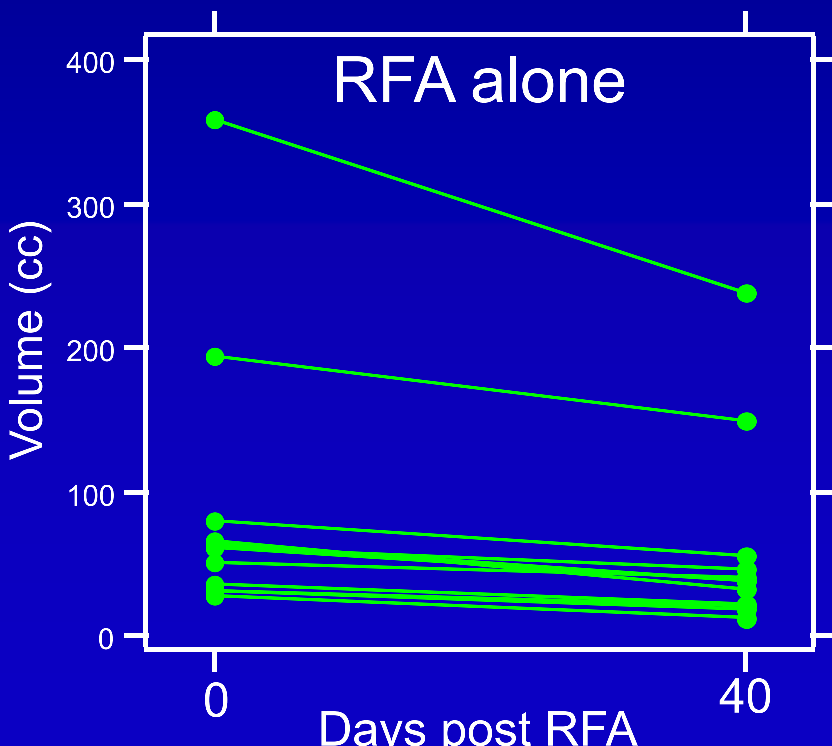


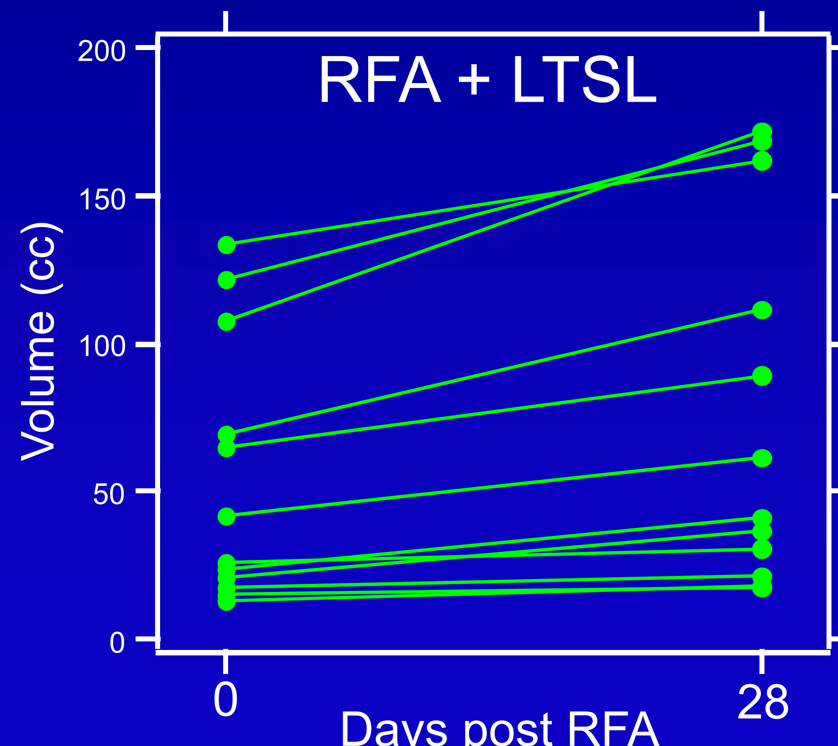


Drug + Device (RFA): Effect on Treated Volumes

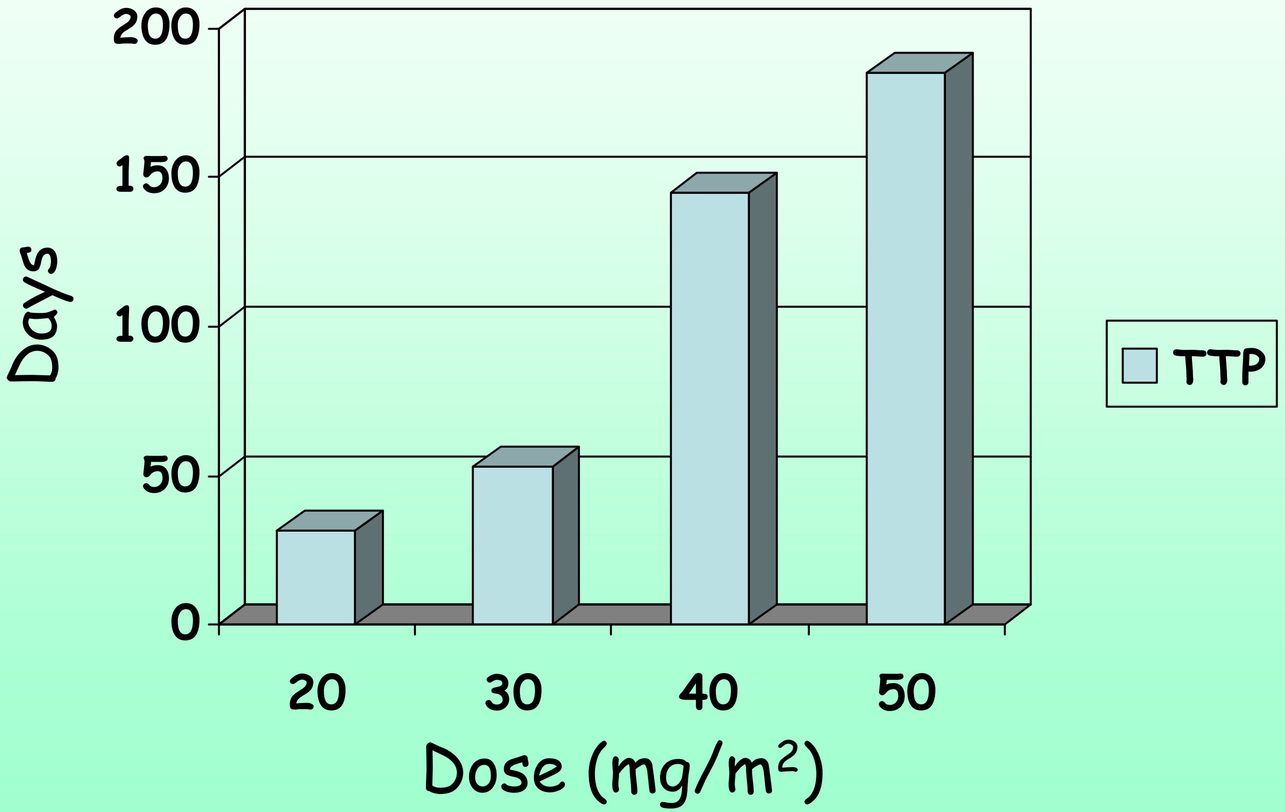
- Bland RFA **-35.8%** volume
- RFA + LTSL +**43.3%** volume







RFA and ThermoDox: Time to progression



Drug eluting beads (DEB)

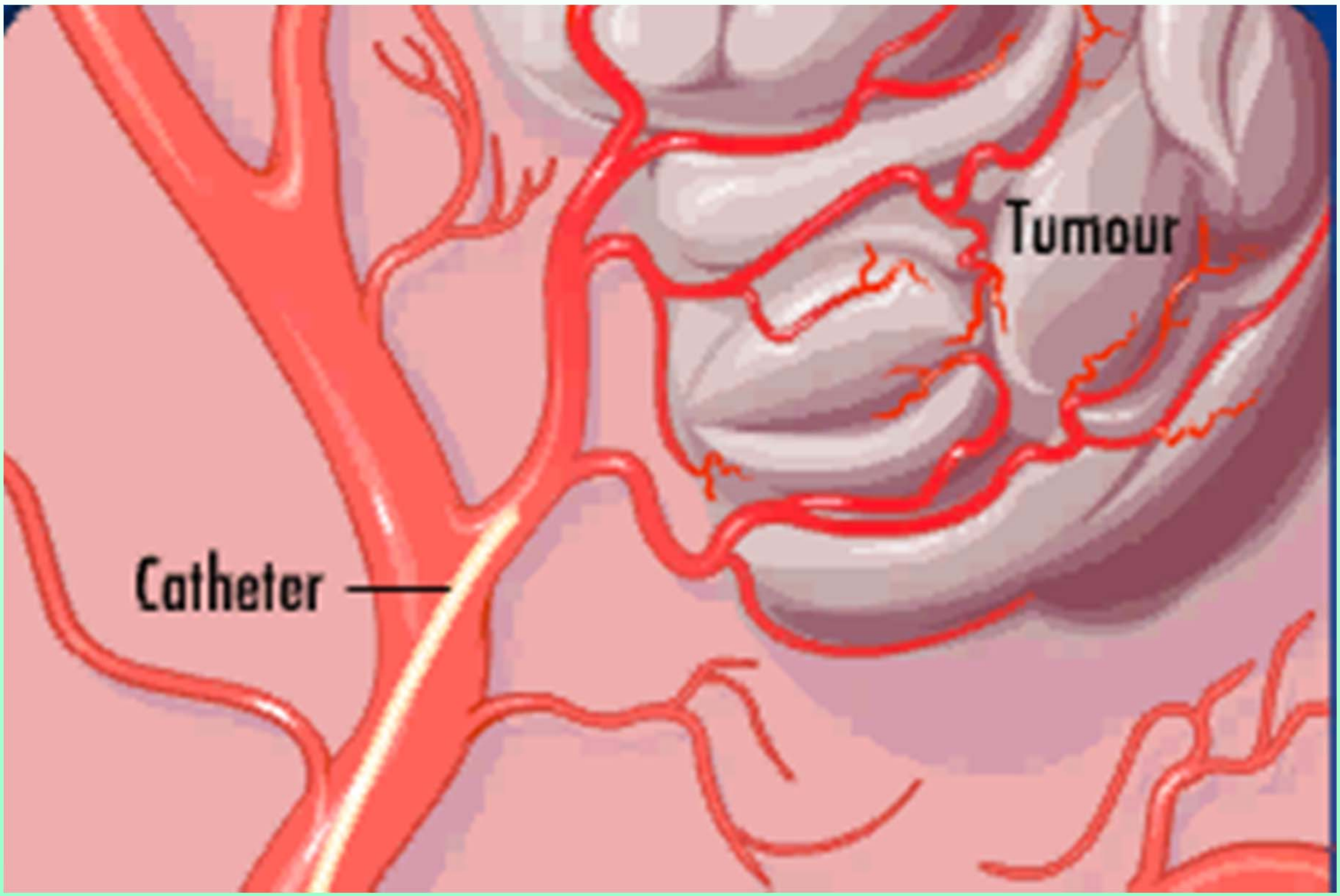
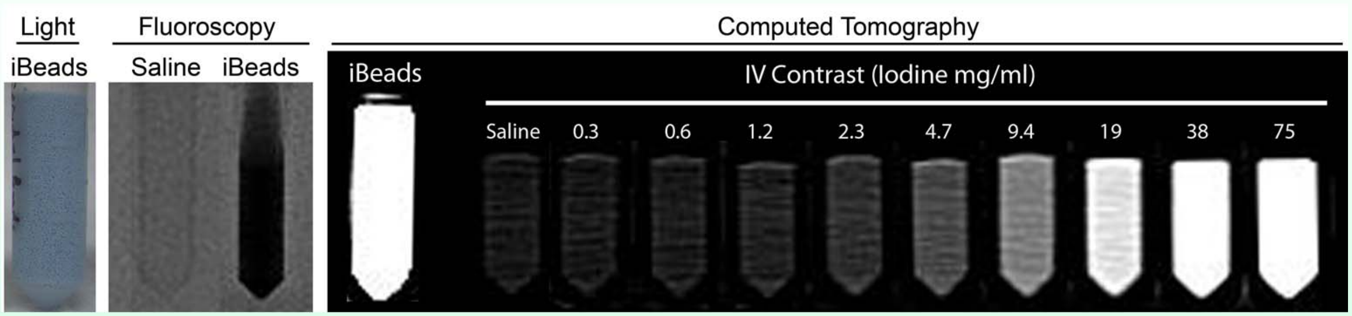
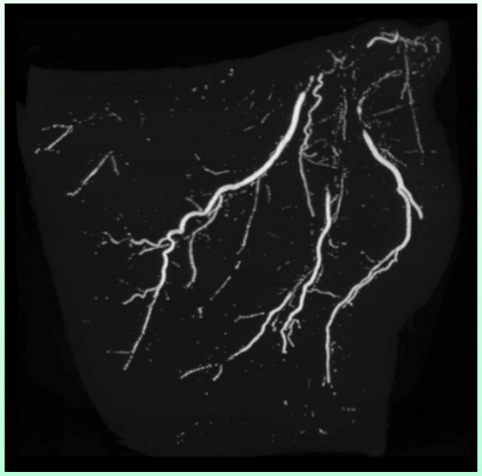
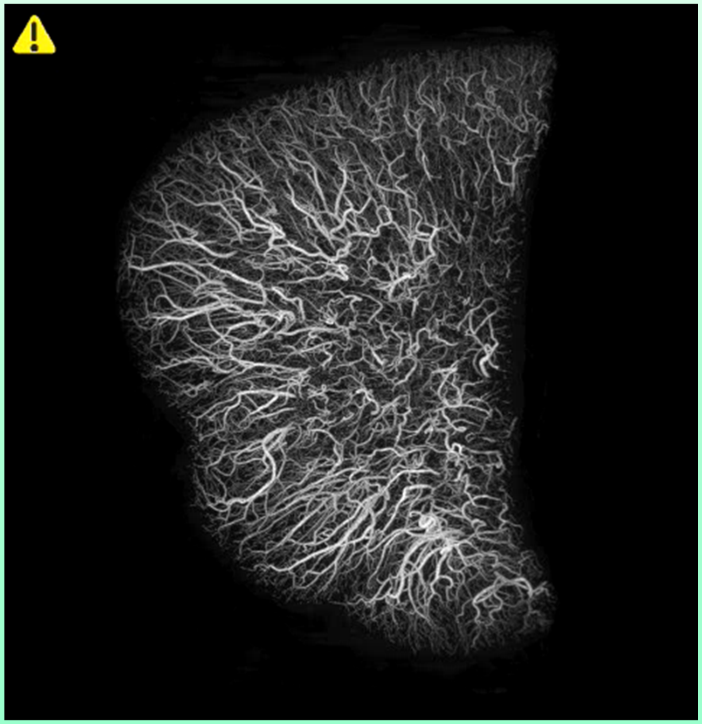


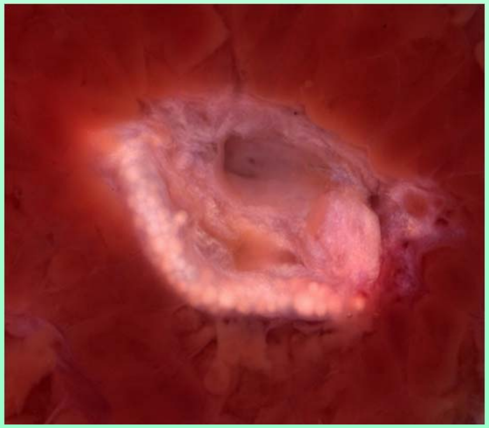
Image-able Drug Eluting Beads:

Pre-clinical, bench, in-vivo



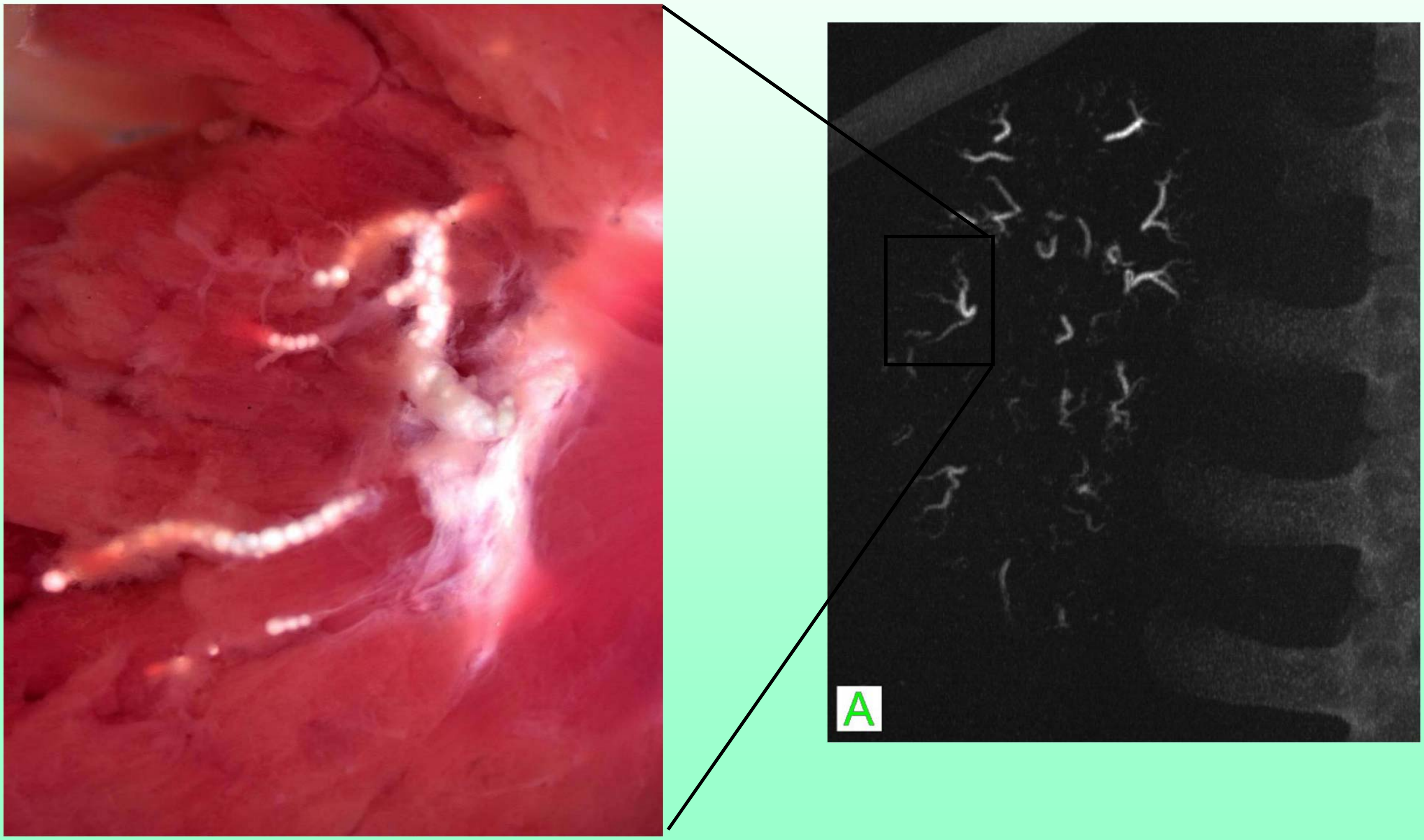






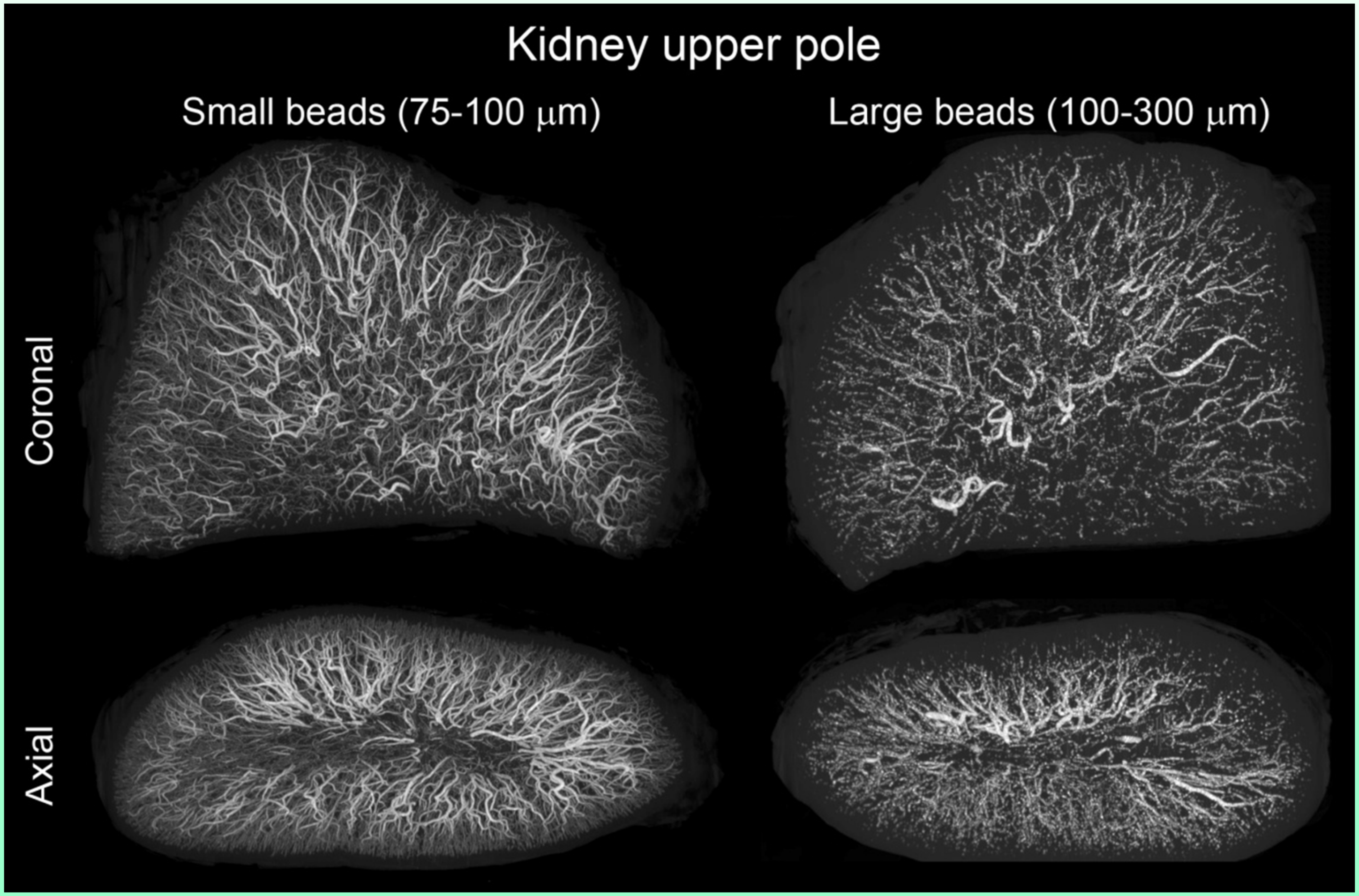
Imaging Drugs for Local Drug Dosing: personalized oncology

Distribution of bead correlates w/ true bead location (image)



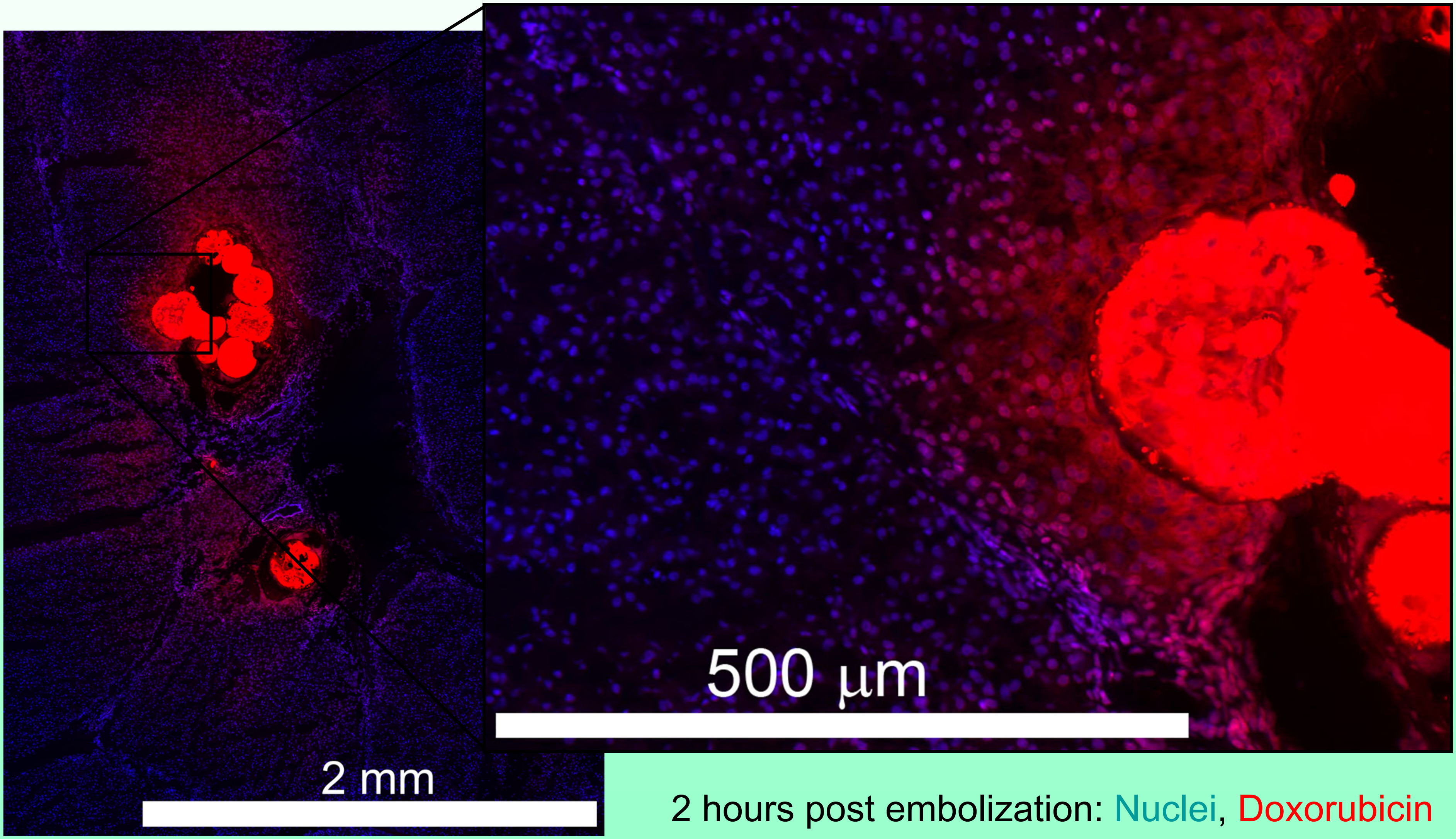
The spatial distribution of embolization beads is directly related to bead size on micro-CT

- Small image-able beads (75-100 µm) found in smaller & peripheral arteries w/ many orders of branching
- Larger beads (100-300 µm) go central w/ gaps between embolized arteries



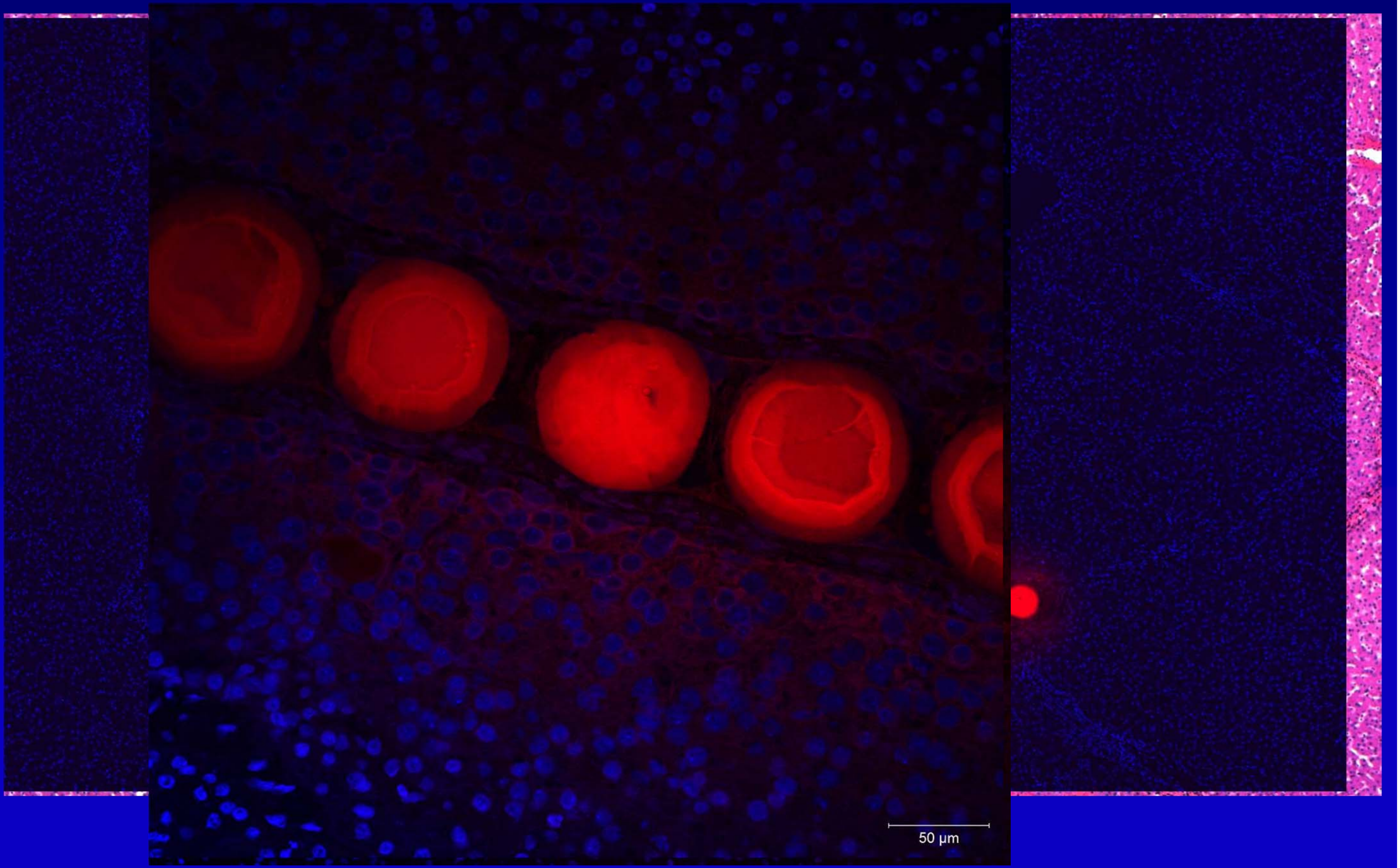
Imaging Dynamic Drug Delivery:

Distribution of drug correlates w/ bead location



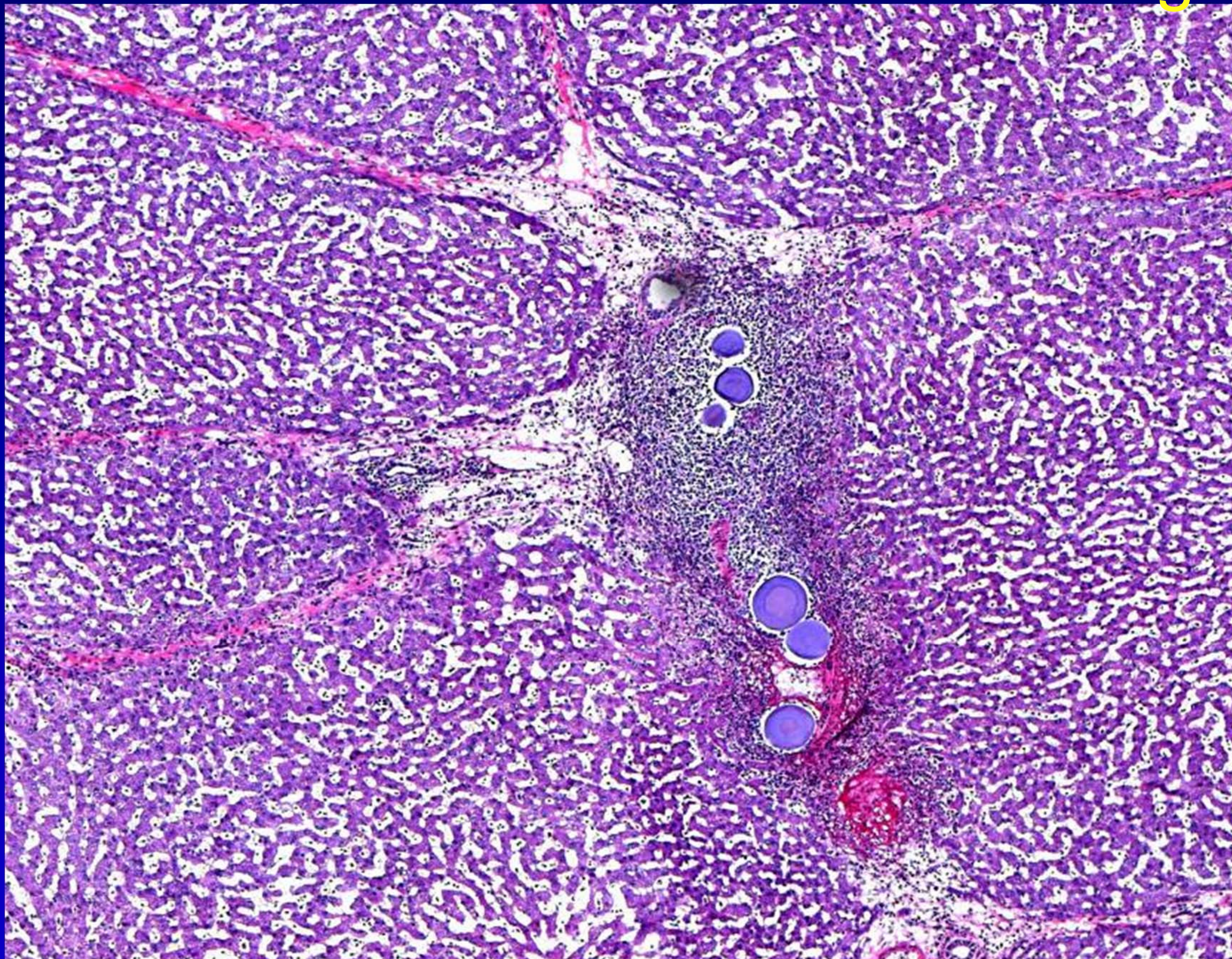
2 hours post embolization: Nuclei, Doxorubicin

30 Minutes Post Small Beads



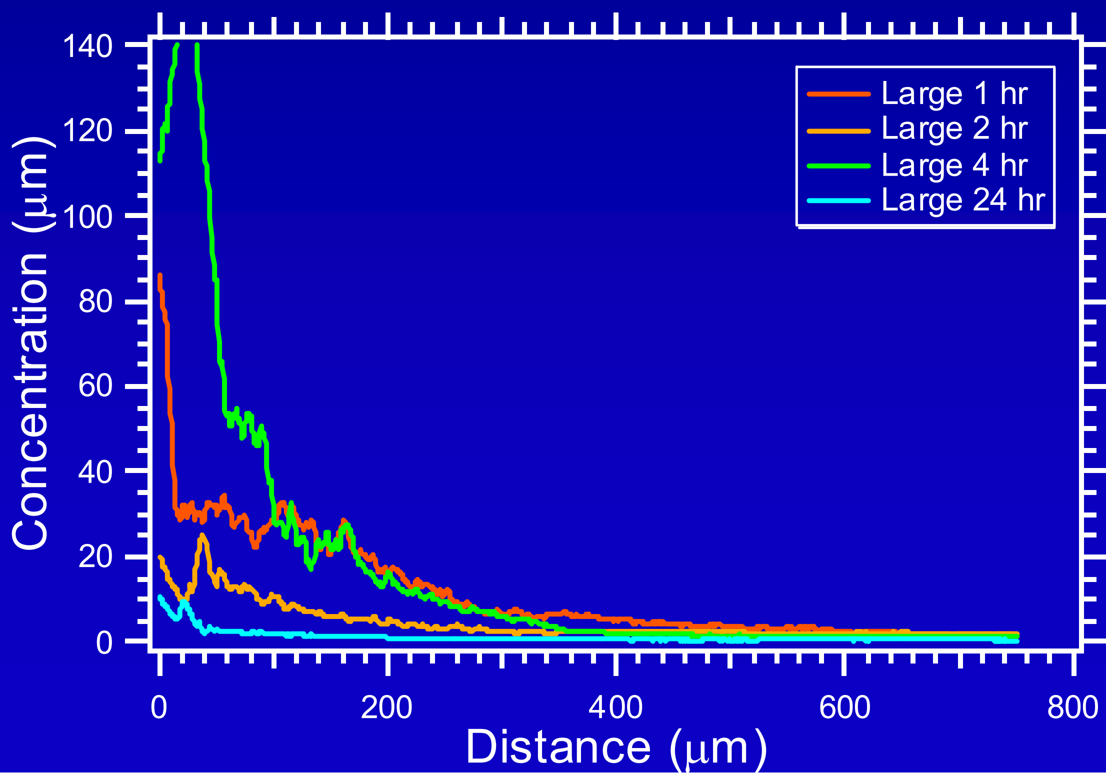
24 Hours Post:

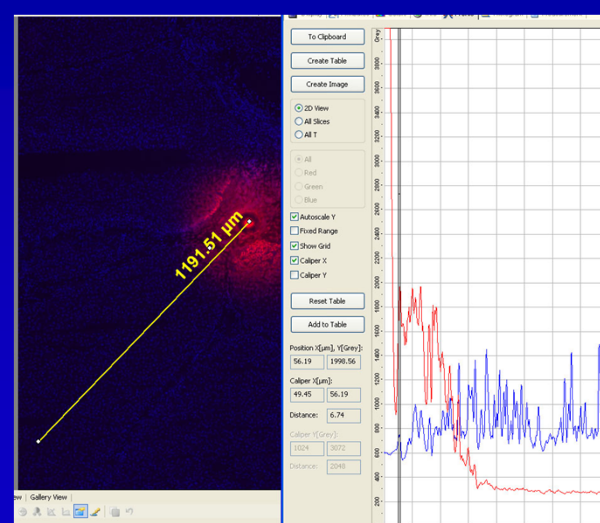
Necrosis colocalizes with drug



Doxorubicin Line Profile for Spatial Drug Quantification

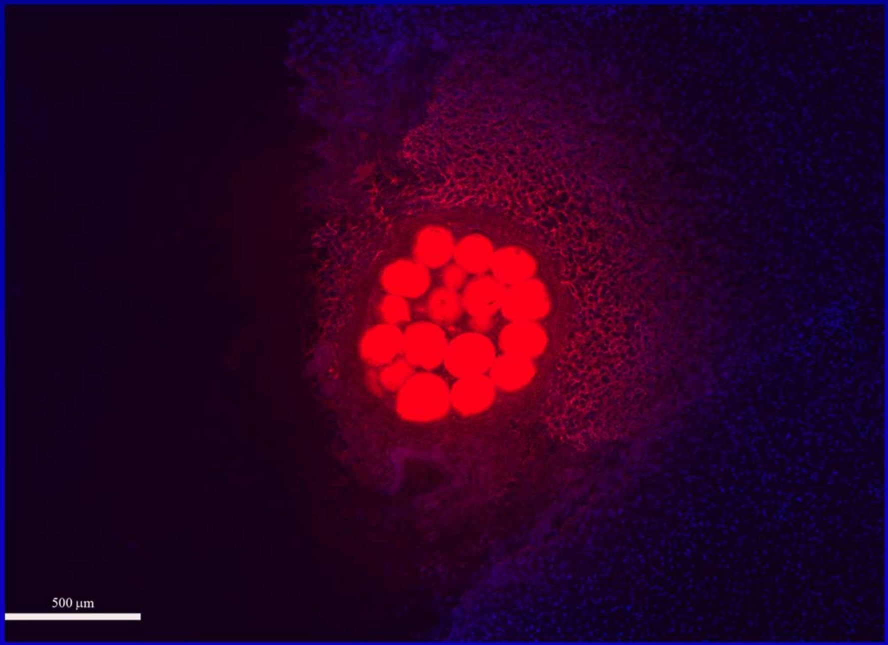
- Dox concentration is highest around beads
- Greatest concentration appears at 4 hrs
- Limited Dox at 24 hrs

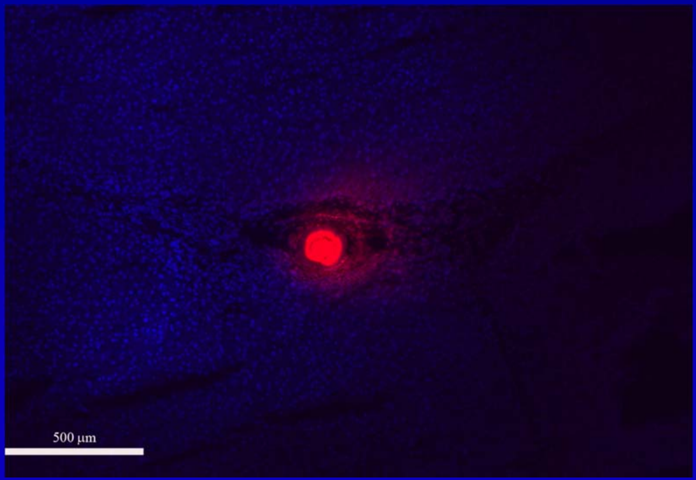




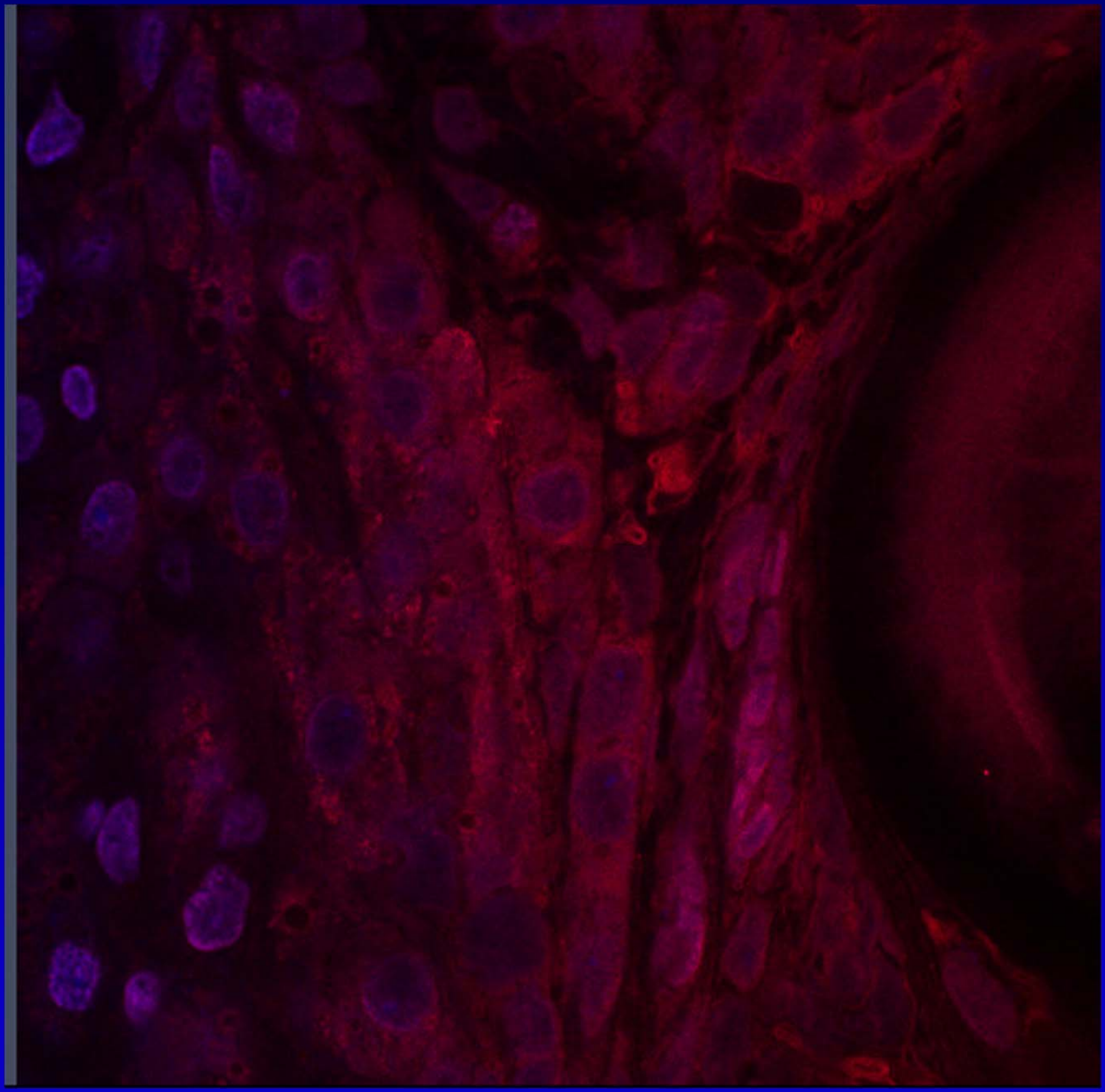
Comparison of one & many beads

- Greater concentration of Dox around more beads





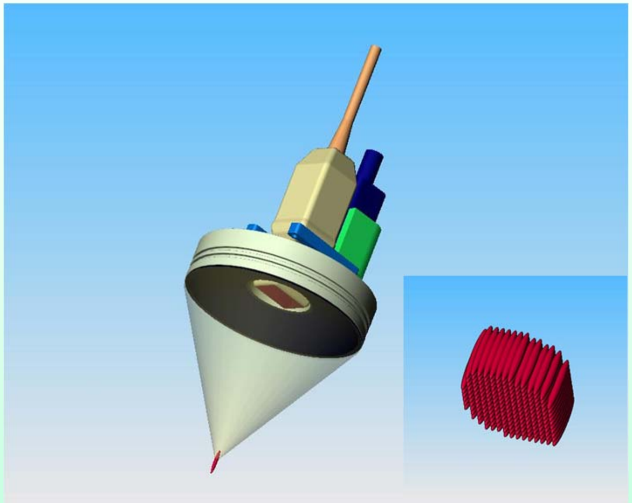
2 Hr Confocal Microscopy – subcellular distribution

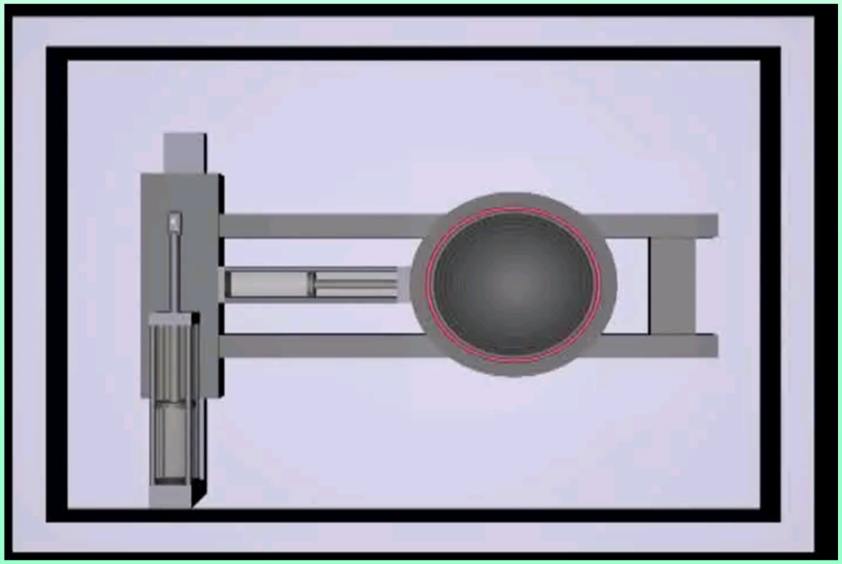


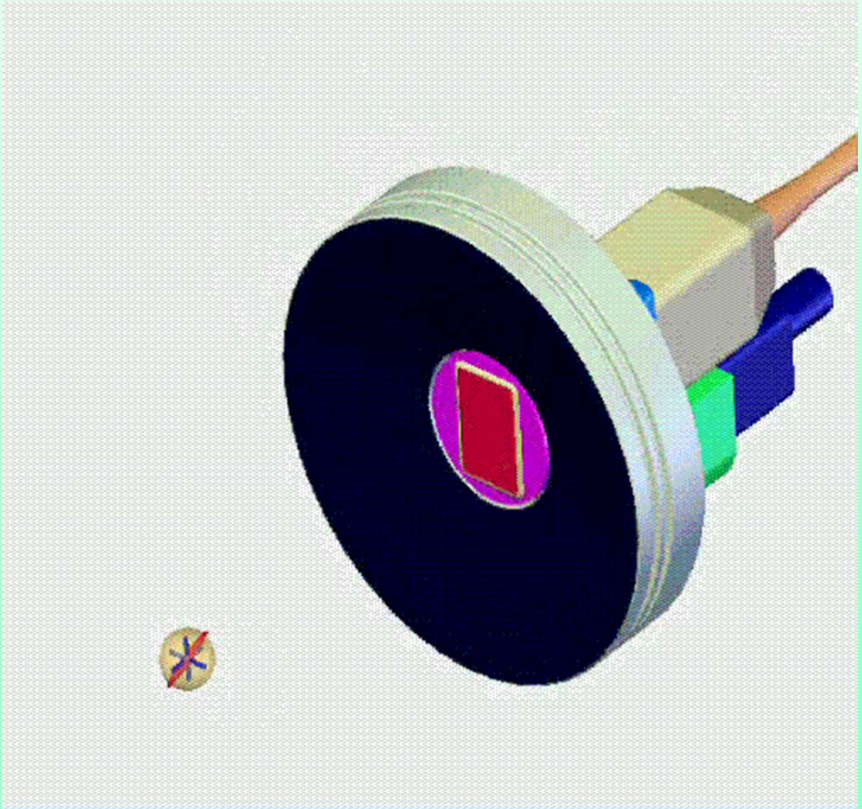
Pre-Drug Eluting Beads (DEB)

4 Weeks Post- DEB

Image Guided, Non-Invasive HIFU for Tissue Destruction, Drug Delivery, or Hyperthermia





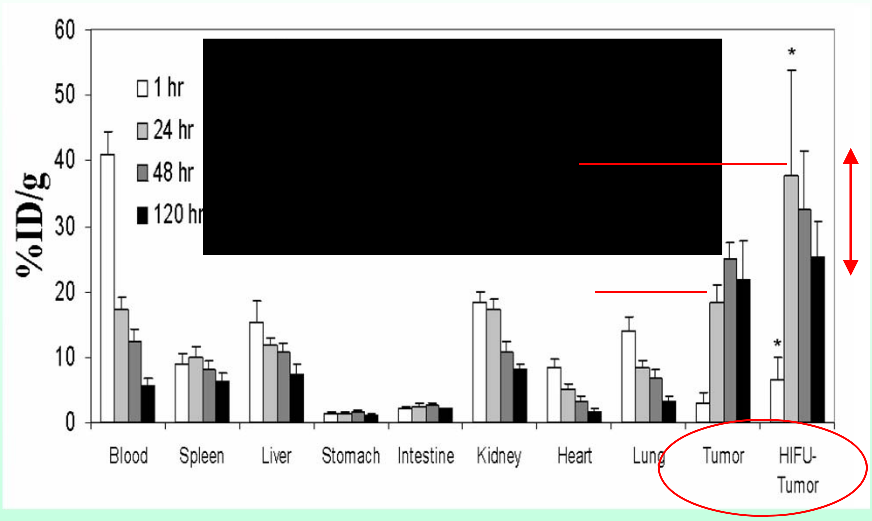


Pulsed HIFU enhanced delivery:

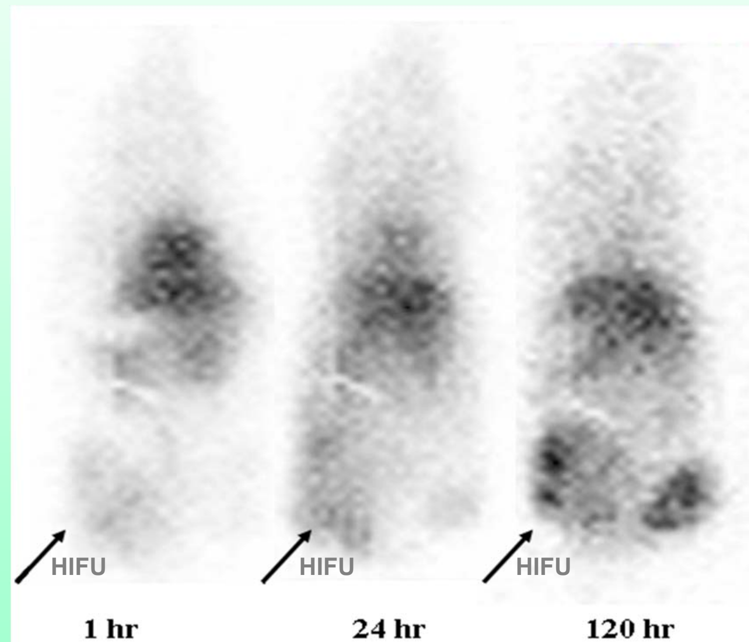
MR contrast agent (Gd)	muscle (rabbits)
FITC-dextran (500 kDa)	SCC7 tumors (mice)
fluorescent Nanoparticles	JC tumors (mice)
Genes - GFP (naked DNA)	SCC7 tumors (mice)
ThermoDox ✹ growth inhibition	mice
Velcade ✹ growth inhibition	mice
TNFa ✹ growth inhibition	SCC7 tumors (mice)
Radiolabled B3 Lewis Y Antibodies	

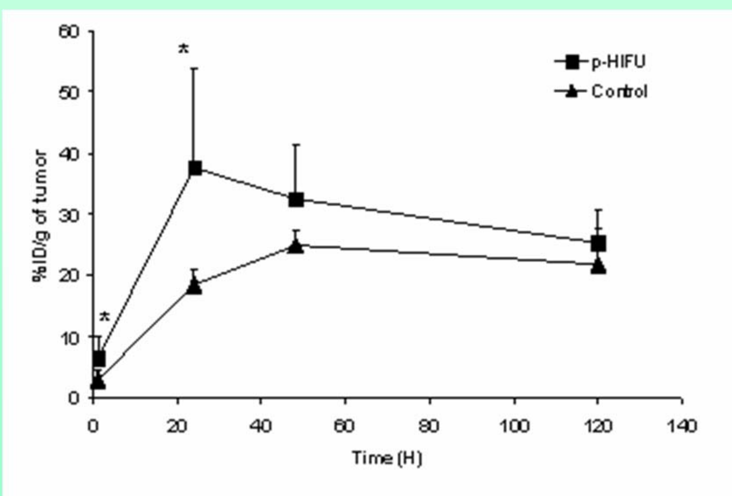
Frenkel, NIH

Enhanced (systemic) delivery of Indium labeled monoclonal antibody in a human Epidermoid tumor model



systemic administration (tumors)

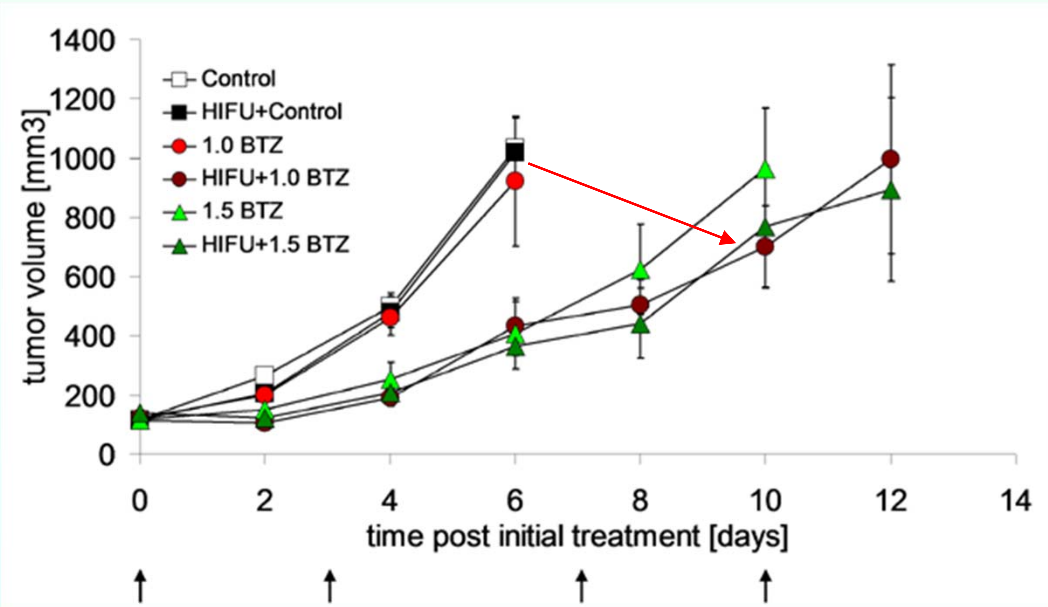


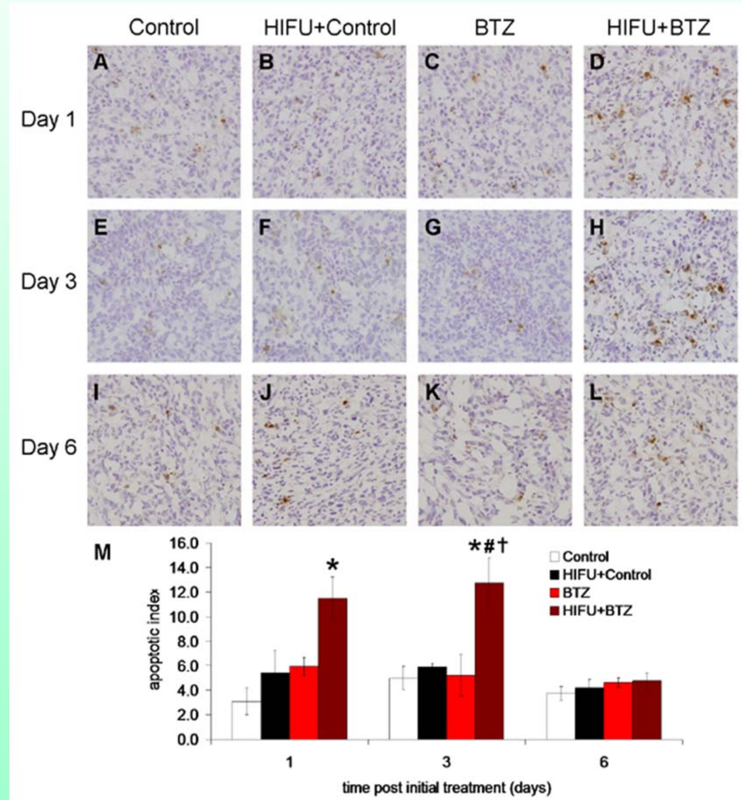


Khaibullina et al 2008 J Nuc Med

Enhanced inhibition of tumor growth: HIFU + drug with narrow therapeutic window -Bortezomib (Velcade®)

systemic administration

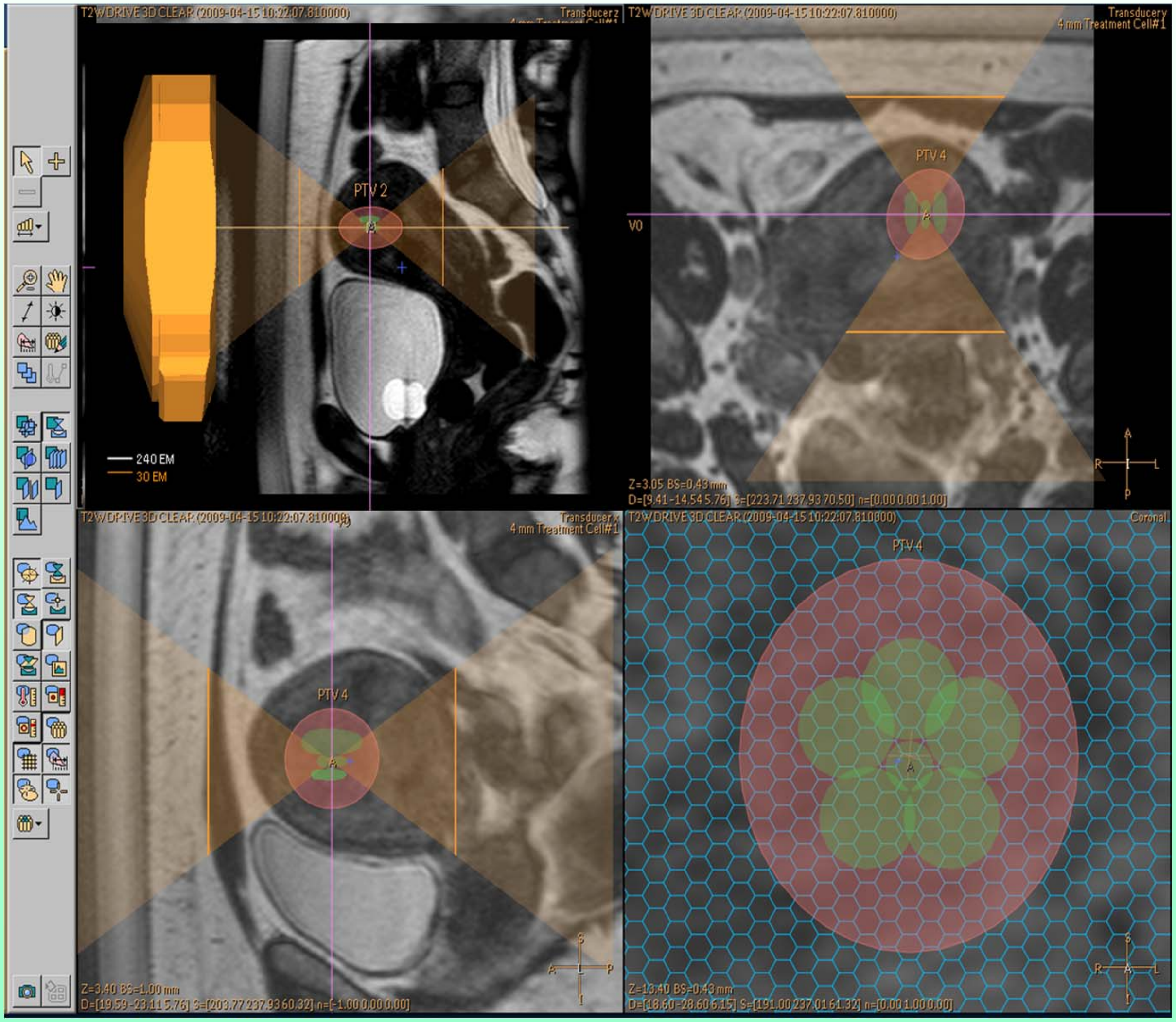


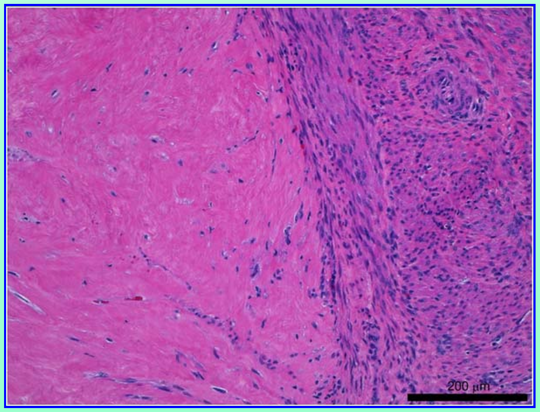


Poff , Radiology

HIFU Thermal Ablation:

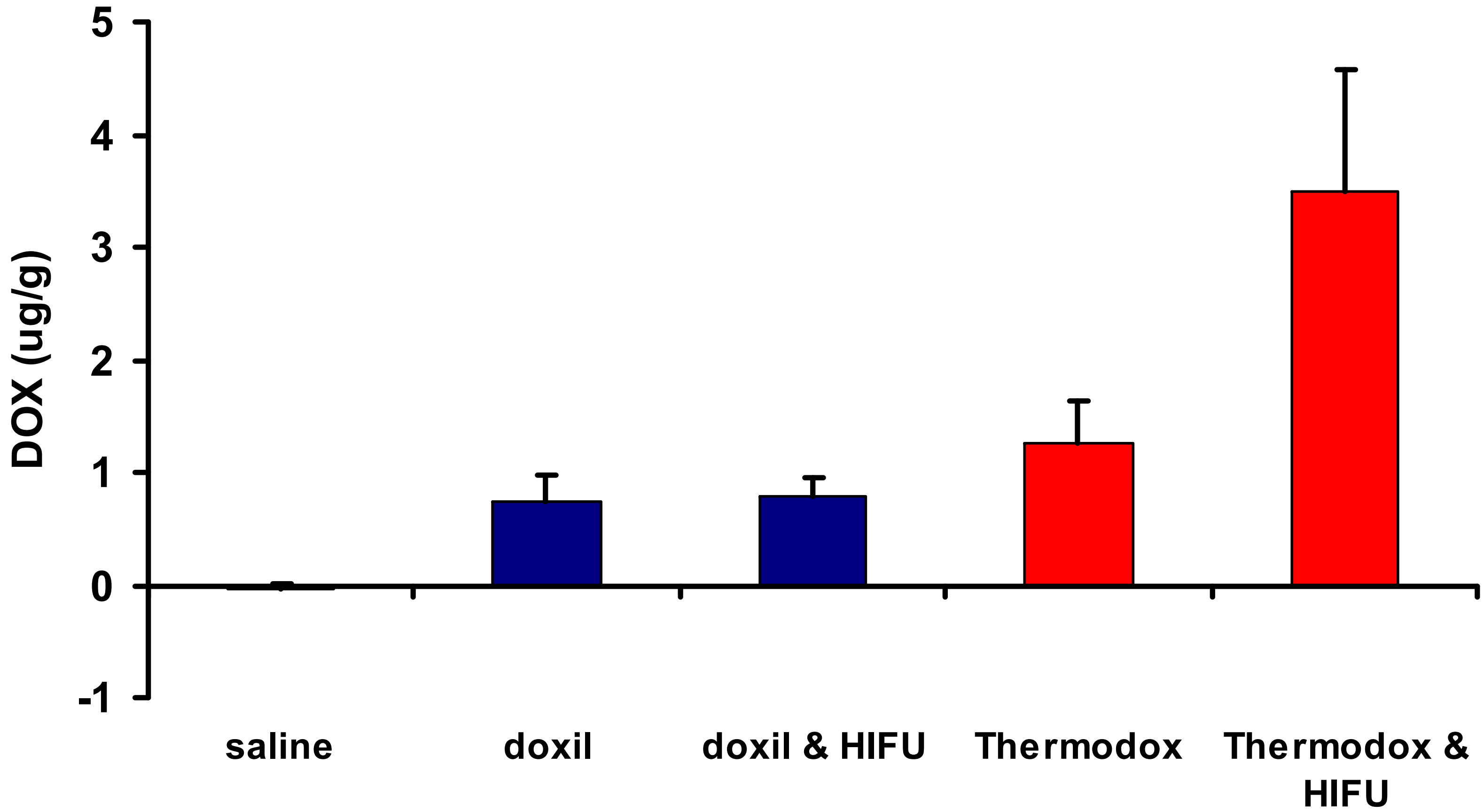
MRI Thermometry to Sculpt Treatment





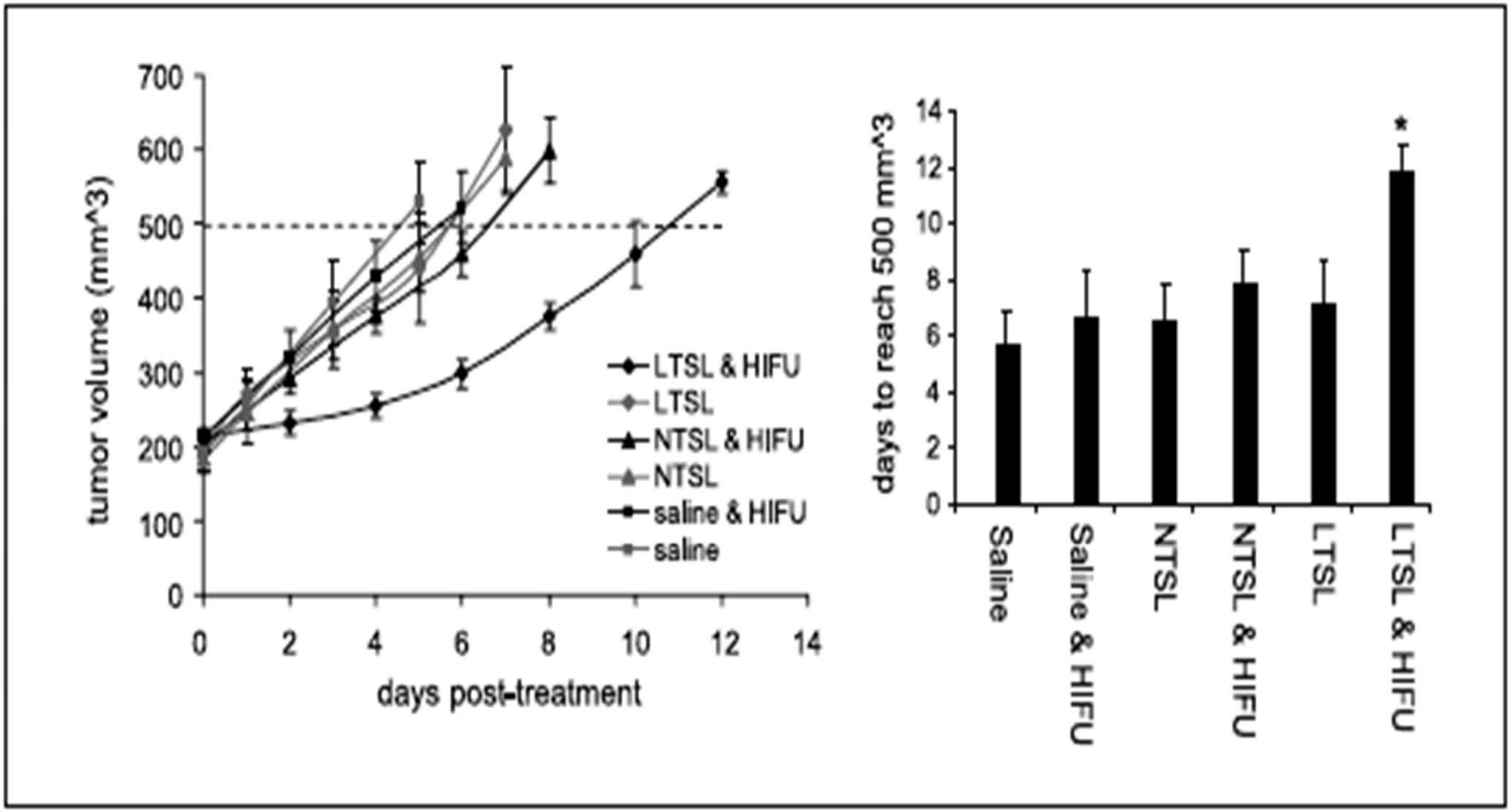
HIFU + Thermodox™

Deposits more drug than HIFU + Doxil ™



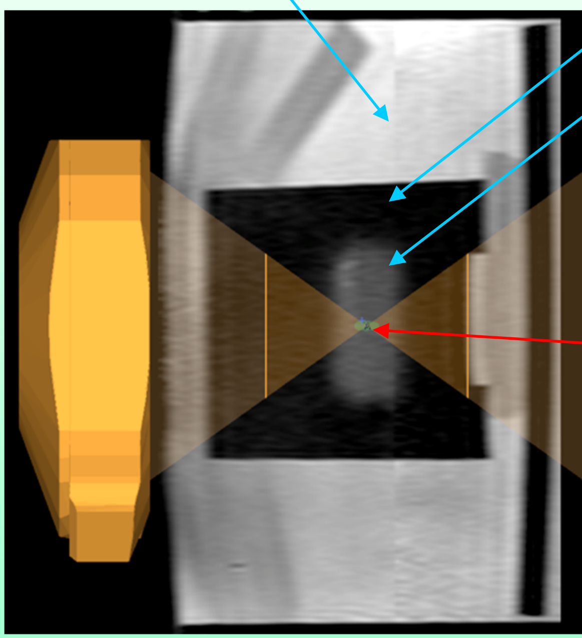
Clin Cancer Res 2007

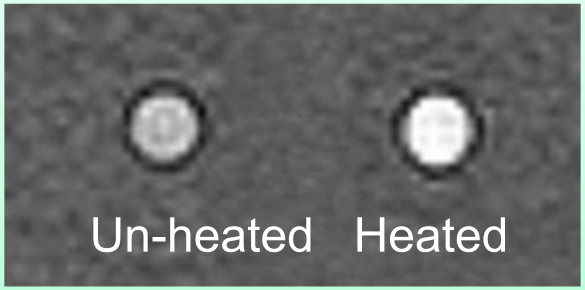
HIFU + Thermodox™ vs HIFU + Doxil ™ Regression Study



Clin Cancer Res 2007

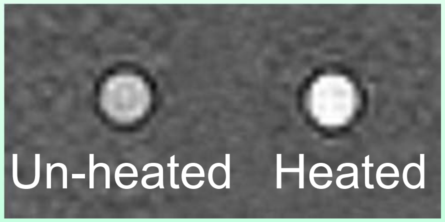
"Drug Dose Painting"
w/ MR-Image-able,
Heat-deployed Liposome

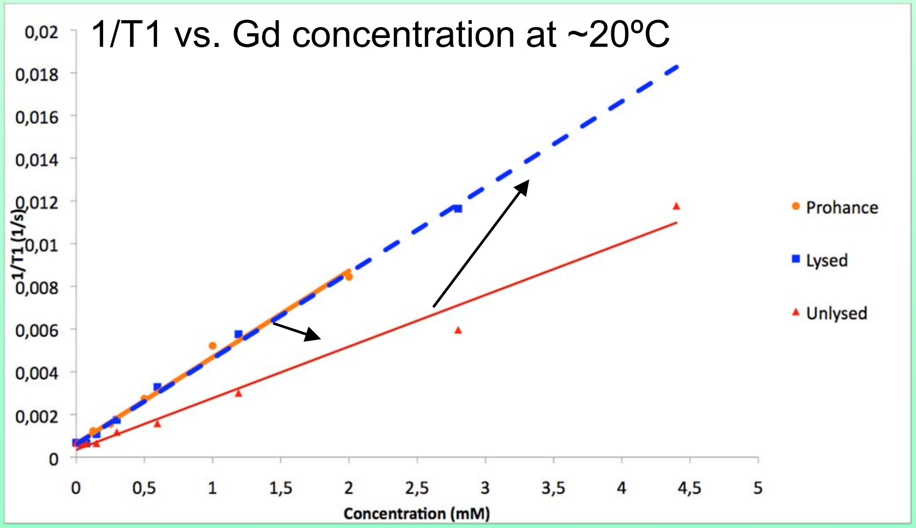




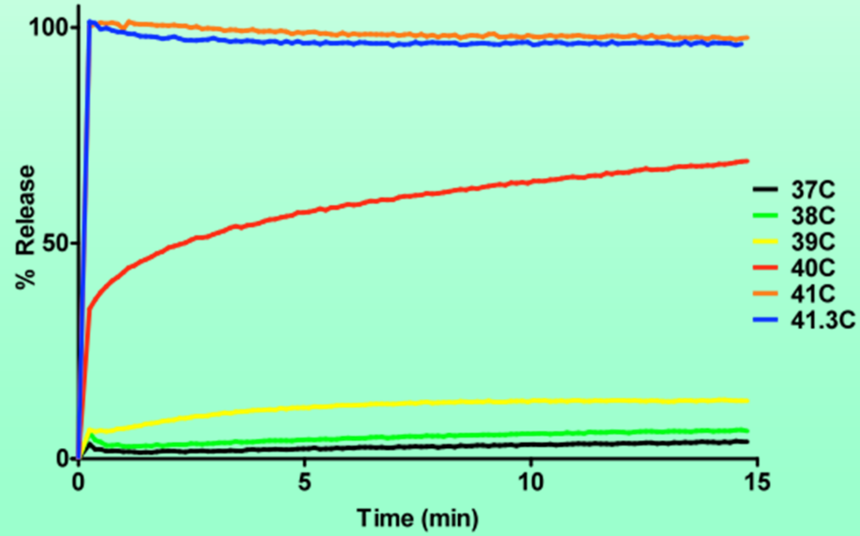
MR-Image-able, Heat-deployed Liposome

- 1/T1 linear function of Gd concentration
- Can differentiate lysed carrier from non-lysed on MRI
- Relaxivity of heated LTSL increased 66% (2.4 vs. 4.0 $Mm^{-1}s^{-1}$)

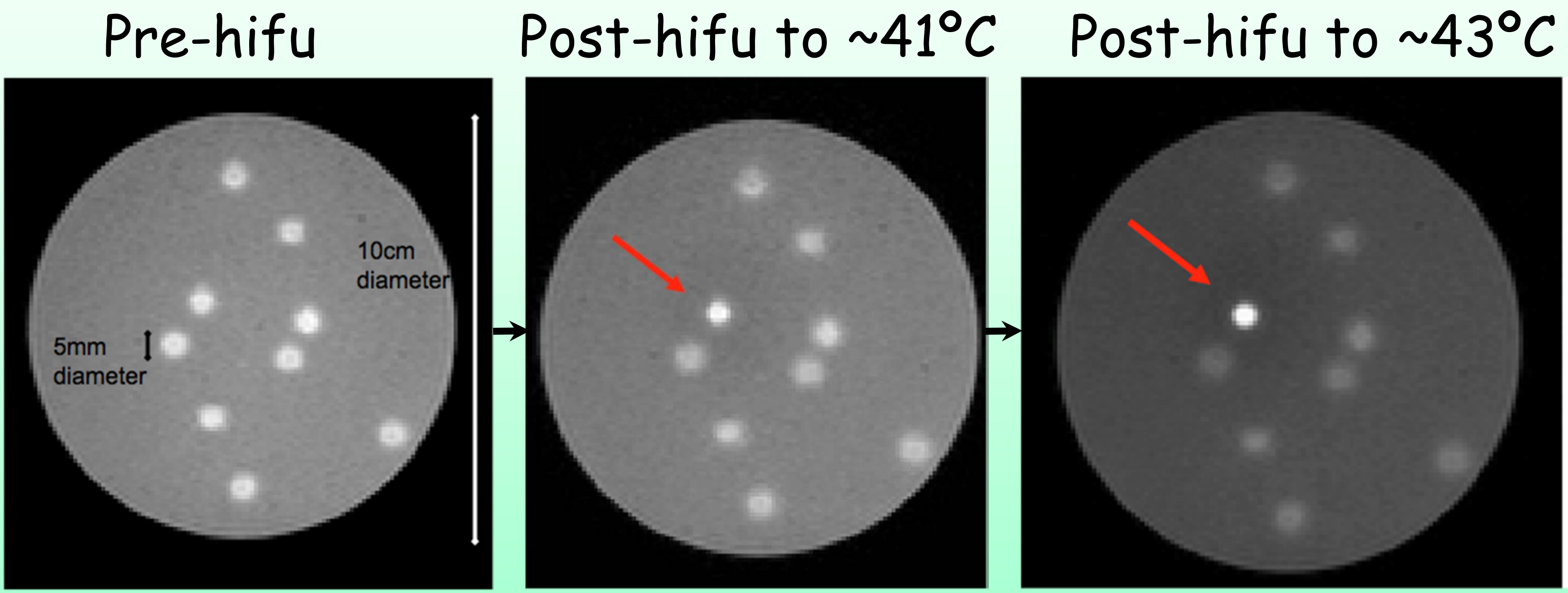




Maximum (and rapid) release of Dox was observed at **temperatures above 41ºC** as measured by spectrofluoroscopy



HIFU causes release of contrast & drug



•Same Gd concentration

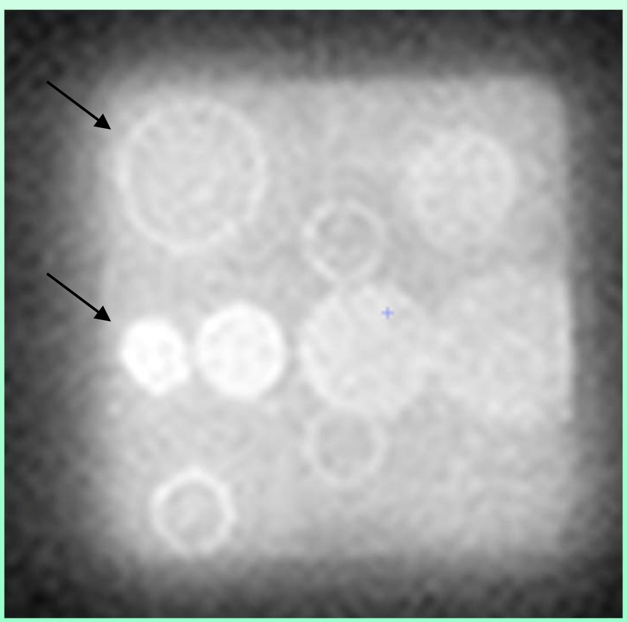
•Equal signal intensity baseline

•Noticeably higher signal

•Much higher signal

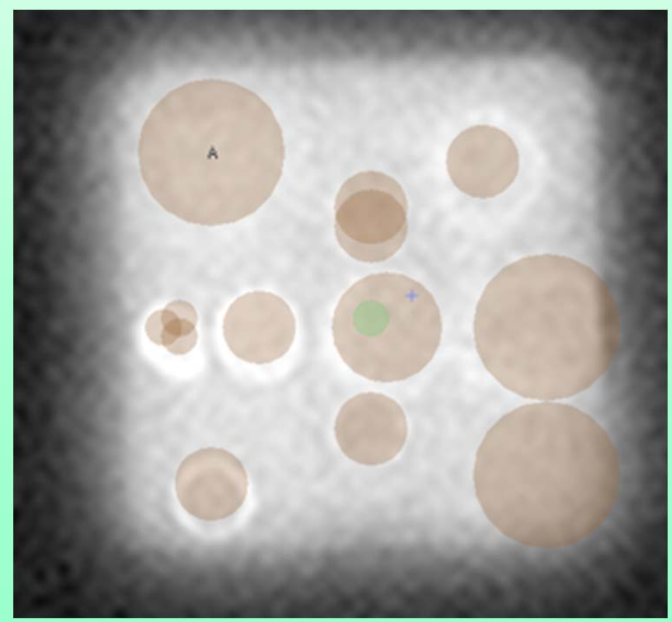
MR-HIFU w/ image-able heat-deployed liposomal carriers

- Real-time monitoring
- Precise spatiotemporal control of content release
- Noninvasive monitoring of contrast release, temperature, & potential for drug delivery assesment
- No cavitation

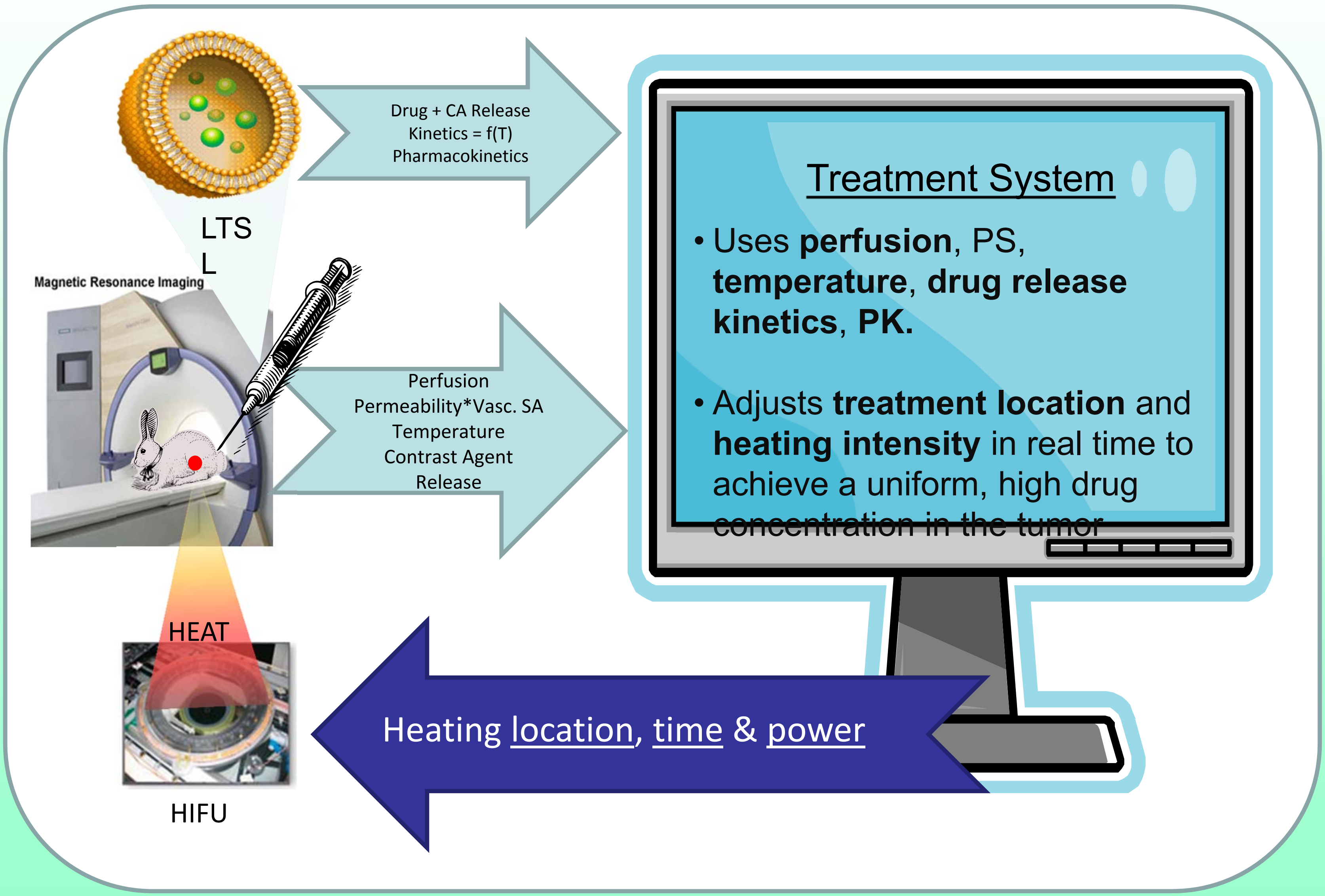


Locations of release in phantom

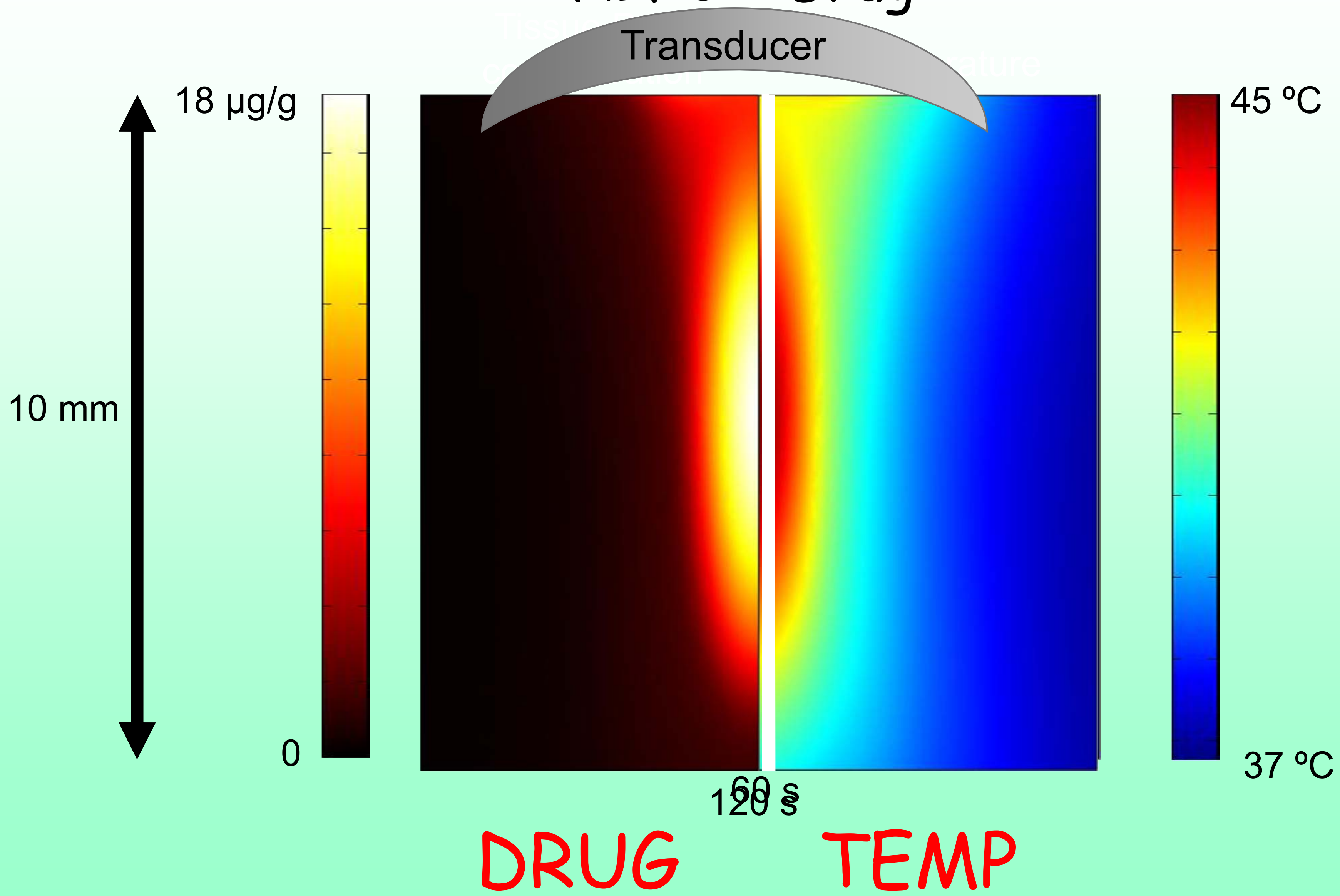
... overlayed with positions of prescribed cells



Feedback-controlled Liposomal Drug Delivery w/ MRI Guided HIFU

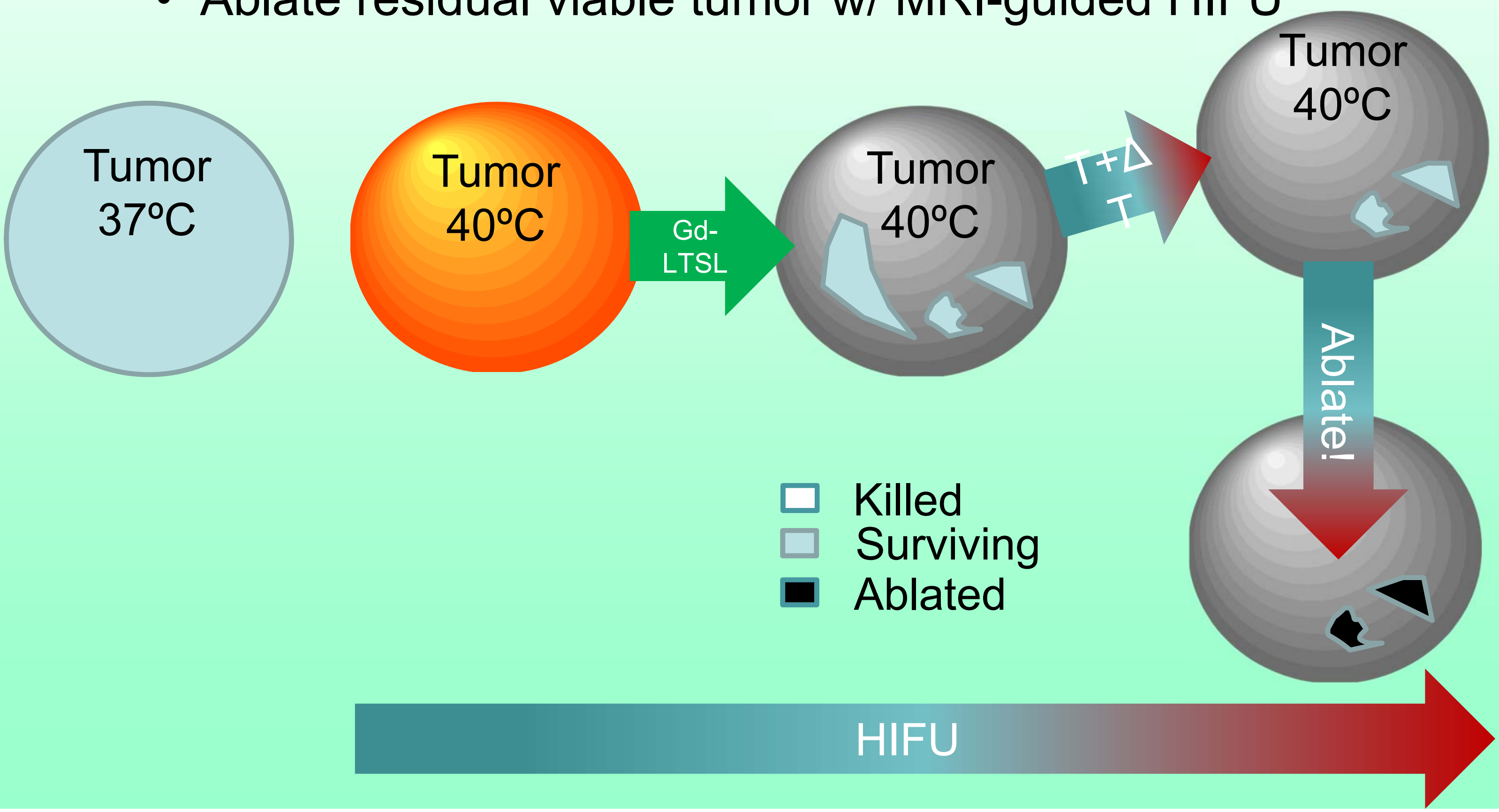


Paired heat transfer pk model:
HIFU + Drug



Modify HIFU for hyperthermia, drug delivery, & thermal ablation

- Poorly perfused regions → poor delivery of drug
  - **Solutions:**
    - Adjust T to perfusion for homogeneous delivery
    - Ablate residual viable tumor w/ MRI-guided HIFU

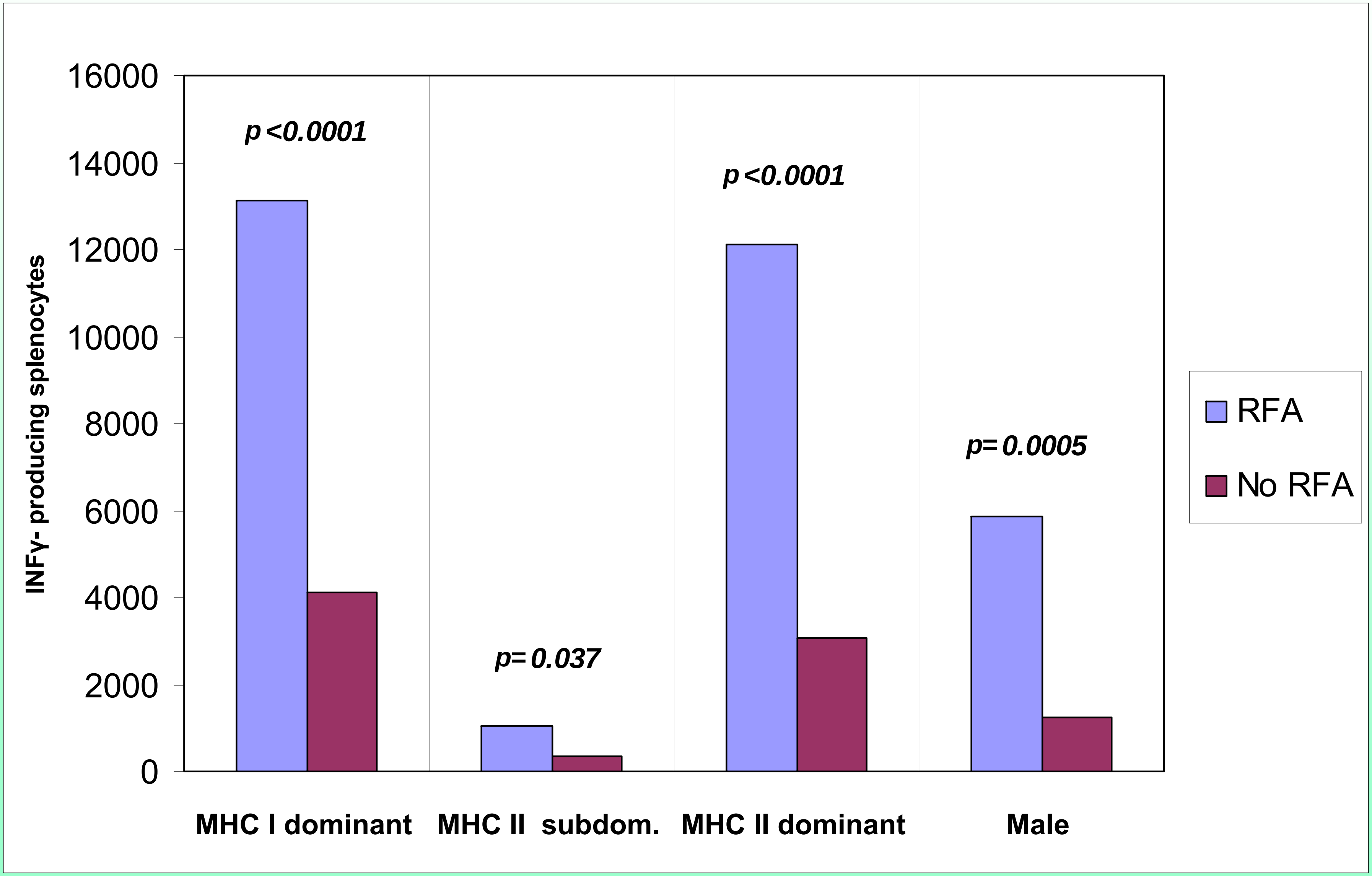


Tissue Alteration: Immunotherapy

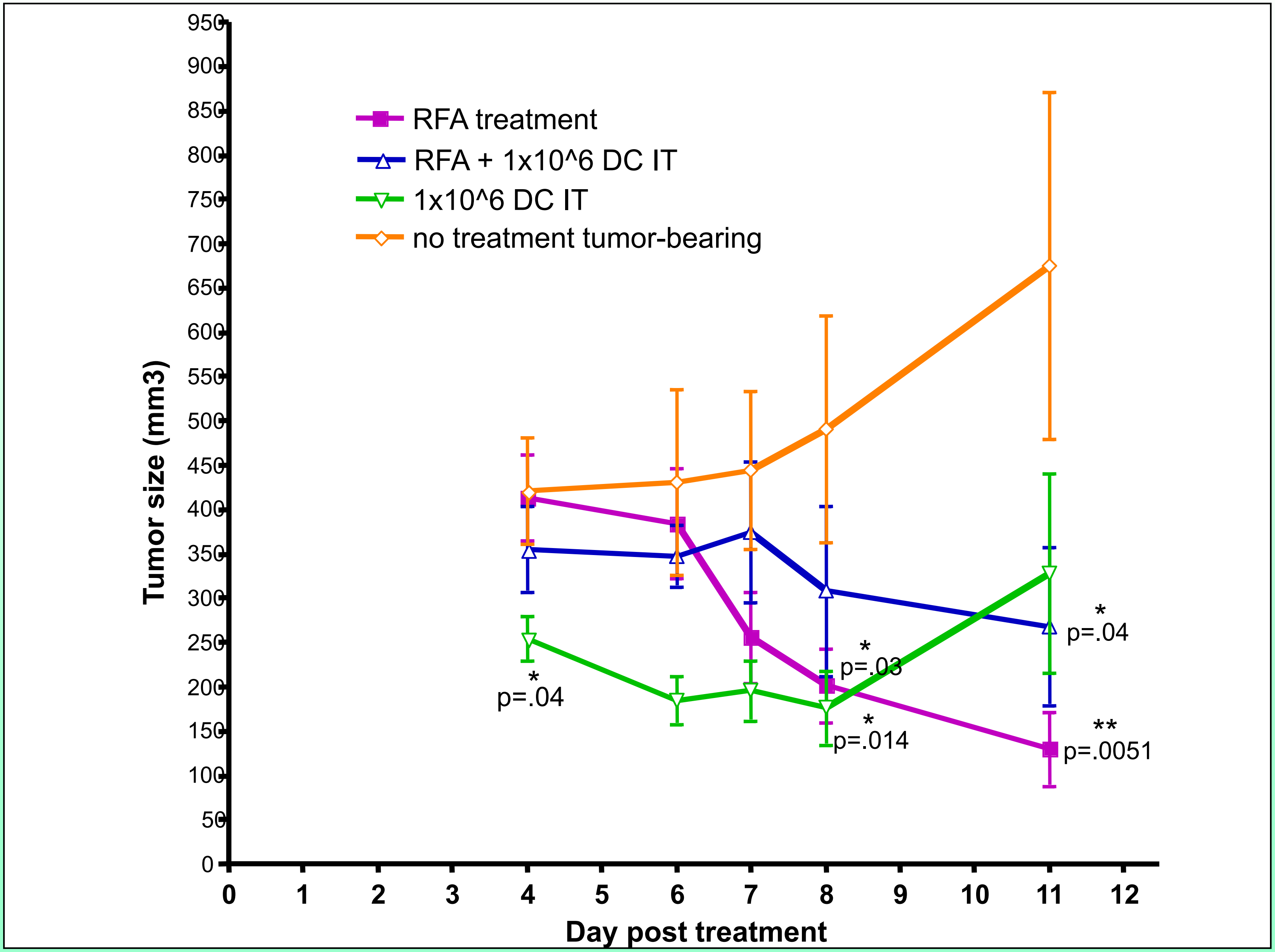
Pre-RFA

2 months Post RFA

Tumor Specific Response

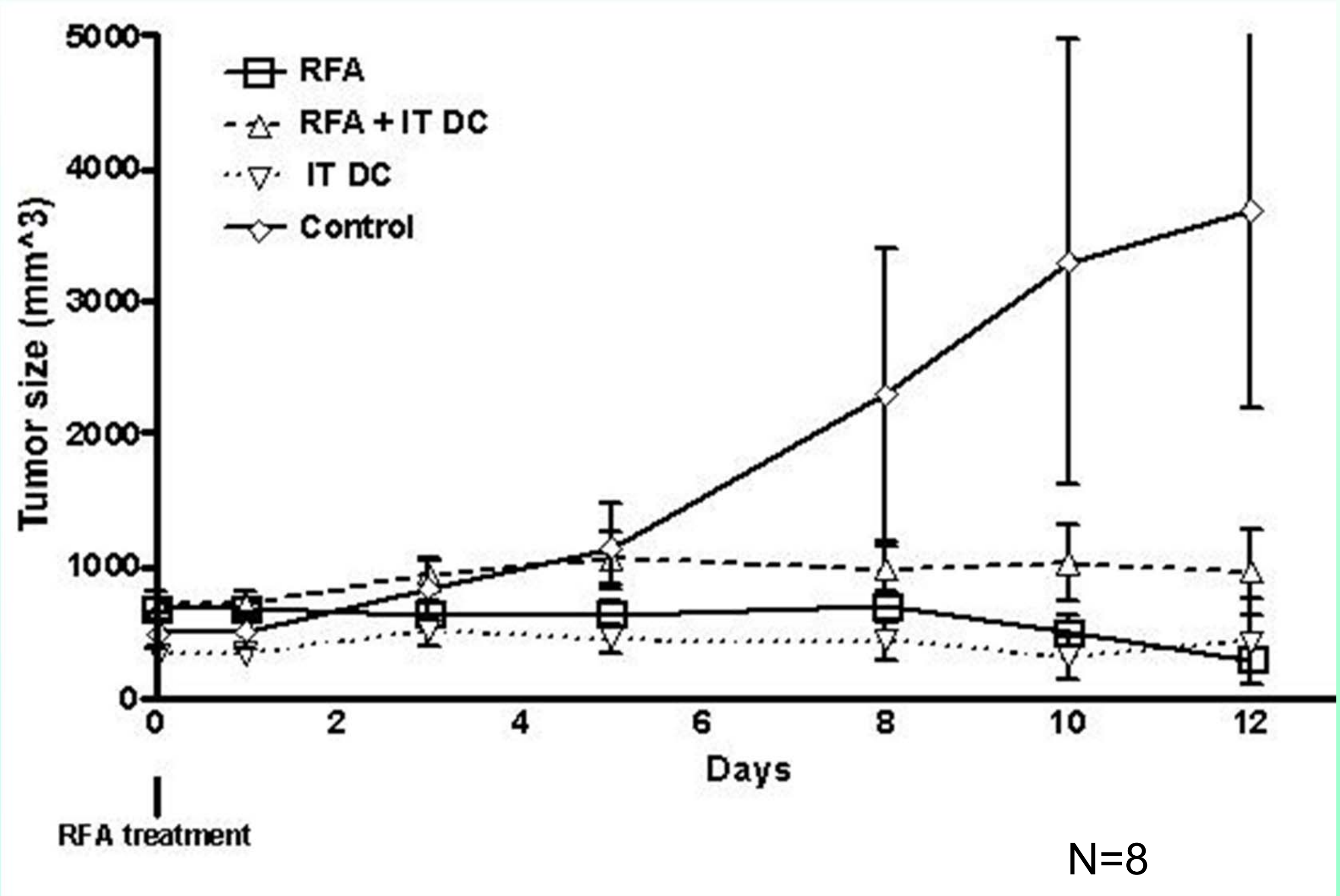


Results: Tumor regression



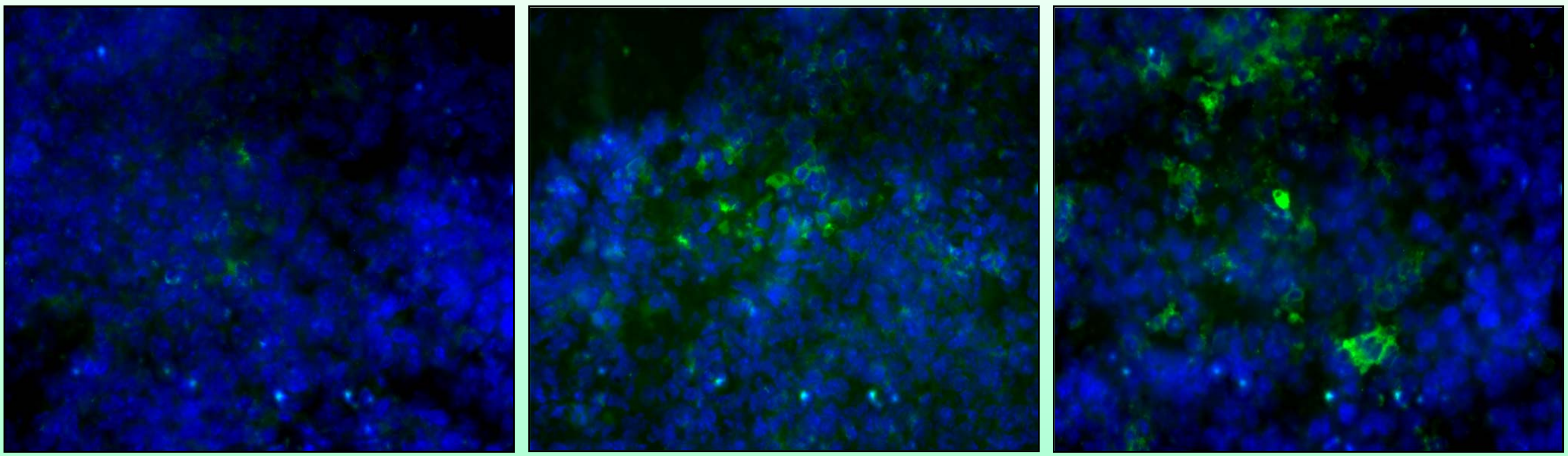
Re-challenge

Adoptive transfer
confer tumor immunity



RFA Induces APC infiltration & amplification of tumor-specific immune response

Control RFA RFA *plus* DC



CD11C IF staining

DAPI (blue) ⇨ nuclei

CD11C (green) ⇨ APC

Team Science

Matt Dreher, Dieter Haemmerich, Ankur Kapoor, Ari Partanen, Jochen Kruecker, Sheng Xu, Sham Sokka, Karun Sharma, Elliot Levy, Aradhana Venkatesan, Nadine Abi-Jaoudeh, Mark Dewhirst, Pavel Yarmelenko, Julie Locklin, Neil Glossop, Peter Pinto, Marston Linehan, Kevin Camphausen, Aradhana Kaushal, James Pingpank, John Karanian, Bill Pritchard, Alberto Chiesa, Itzhak Avital, Udai Kammula

National Institutes of Health

National Cancer Institute

FDA

National Heart Lung and Blood Institute — People Science Health

NIBIB

GORE

PHILIPS

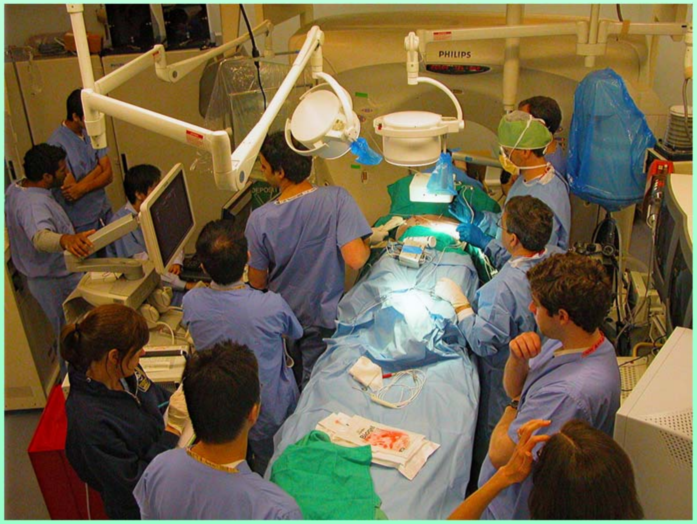
tyco Healthcare

Valleylab

TRAXTAL

CELSION

The Biocompatibles Foundation — Research Innovation Education



http://www.cc.nih.gov/centerio/index.html